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## Clinical manifestations and diagnosis of celiac disease in children

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**INTRODUCTION** — Celiac disease (also known as gluten-sensitive enteropathy or nontropical sprue) is an immune-mediated inflammation of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically sensitive individuals. The disorder is common, occurring in 0.5 to 1 percent of the general population in most countries [1].

The grains that contain the triggering proteins are wheat, barley, and rye; there is some controversy as to whether oats also can cause the disease. The small intestinal mucosa improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. In a study from an era in which celiac disease was not treated, mortality was 12 percent [2]. The appropriate treatment is a gluten-free diet for life, and this results in complete resolution of symptoms for most individuals.

The diagnosis and clinical manifestations of celiac disease are reviewed here. Its management and the use of antibodies for diagnosis are presented separately. (See "[Management of celiac disease in children](#)" and "[Diagnosis of celiac disease](#)".)

This topic also is discussed in an official position statement issued by the American Gastroenterological Association [3] and a consensus statement from the National Institutes of Health [4]. The discussion below also reflects guidelines developed by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [1]. The pediatric guidelines are available on the NASPGHAN Web site ([www.naspghan.org](http://www.naspghan.org)).

**PATHOGENESIS** — The cause of celiac disease was unexplained until the Dutch pediatrician Willem K Dicke recognized an association between the consumption of bread and cereals and relapsing diarrhea. This observation was corroborated when, during periods of food shortage in the Second World War, the symptoms of his

patients improved once bread was replaced by non-cereal-containing foods; this finding confirmed the benefit of earlier, empirical diets that used pure fruit, potatoes, banana, milk, or meat [5-7].

Because symptoms reoccurred when bread was reintroduced after the war, Dicke and van de Kamer initiated controlled experiments exposing children with celiac disease to defined diets and then determined fecal weight and fecal fat as a measure of malabsorption. Wheat, barley, rye, and (to a minor degree) oats triggered malabsorption, which could be reversed after exclusion of these "toxic" cereals from the diet [8]. Shortly thereafter, the toxic agents were found to be present in gluten, the primary protein found in wheat [9].

The celiac lesion in the proximal small intestine was first described in 1954. The primary findings were mucosal inflammation, crypt hyperplasia, and villous atrophy ([picture 1](#)) [10]. With the development of peroral biopsy, it became apparent that celiac disease and adult nontropical sprue shared the same features and pathogenesis [11].

**Genetic factors** — Celiac disease is an immune disorder that is triggered by an environmental agent (gluten) in genetically predisposed individuals [12,13]. The genetic basis of the disease is shown by the frequent intrafamilial occurrence and the remarkably close association with the HLA-DQ2 and/or DQ8 gene locus. While the presence of either the HLA DQ2 or DQ8 genotype is essential to confer disease, it is not sufficient, and another gene or genes at a non-HLA locus must also participate. Non-HLA genes are likely to be a stronger determinant of disease susceptibility than the HLA locus.

Because of common genetic contributors, several groups are at increased risk for celiac disease. The genetic contributors to celiac disease are discussed in detail separately. (See '[High-risk groups](#)' below and '[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)', section on '[Genetic factors](#)'.)

**Autoimmunity** — Celiac disease is associated with a number of autoimmune disorders including type 1 diabetes mellitus and autoimmune thyroid disease. In addition, the intestinal lesion of celiac disease is associated with several different autoantibodies that are useful for diagnostic purposes. IgA-antibodies against endomysium and the endomysial autoantigen tissue transglutaminase are highly sensitive and specific. (See '[Associated conditions](#)' below and '[Diagnostic approach](#)' below.)

It is possible that immunologic similarities between gliadin protein motifs and enteric pathogens may be involved in pathogenesis of an immunologic response to antigens in gluten. This hypothesis was supported in one study, in which analysis of alpha gliadin demonstrated an amino acid region that was homologous to the

54KDa E1b protein coat of adenovirus 12, suggesting that exposure to the virus in a susceptible person could be involved in the pathogenesis of celiac disease [14]. (See "[Epidemiology and clinical manifestations of adenovirus infection](#)".)

However, the pathogenetic role of these antibodies remains to be clarified. Both humoral and cell-mediated immune mechanisms are involved, and the range of gluten peptides triggering the reaction may vary with the age of the patient. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Autoantibodies and intraepithelial lymphocytes'.)

**Infant feeding practices** — The pathogenesis of celiac disease at any age requires exposure to gluten. However, there is emerging evidence that the timing and manner of gluten exposure may affect the risk for or clinical expression of celiac disease. Observational studies suggest that the risk for celiac disease might be reduced by continuing breast feeding while introducing gluten into an infant's diet, and by introducing gluten gradually [15,16].

These factors are thought to be implicated in an epidemic of celiac disease that occurred in Sweden between 1984 and 1996, in which the frequency of symptomatic celiac disease in children younger than two years increased four-fold [17]. The onset and end of this epidemic were abrupt, and coincided with specific changes in infant feeding practices. Rates of celiac disease among children born during this epidemic are as high as 3 percent by age 12 [18]. One third of these cases came to attention because of symptoms, and the remaining cases were diagnosed by population screening. Currently, infant feeding practices in Sweden emphasize gradual introduction of gluten while breast-feeding is ongoing, and the prevalence of celiac disease in young children has returned to pre-epidemic levels. Future studies are needed to determine whether these measures decrease the lifetime risk for celiac disease, or merely delay onset of disease.

**CLASSIFICATION** — For many years, celiac disease was defined by a set of classic clinical manifestations. However, the combination of serologic, genetic, and histologic data has led to an appreciation of the highly variable clinical manifestations of the condition and the description of other categories of celiac disease.

**Classic disease** — The classic description of celiac disease, or gluten-sensitive enteropathy, includes the following three features:

- Symptoms of malabsorption such as steatorrhea, weight loss, or other signs of nutrient or vitamin deficiency [11].
- The presence of characteristic histologic changes (including villous atrophy) on small intestinal biopsy.
- Resolution of the mucosal lesions and symptoms upon withdrawal of gluten-

containing foods, usually within a few weeks to months.

The degree of the villous atrophy does not necessarily correlate with the severity of clinical symptoms. Although there is a gradient of decreasing severity from the proximal to the distal small intestine, correlating with the higher proximal concentration of dietary gluten, sampling error can occur due to some inhomogeneity of mucosal inflammation.

The histologic features range from a mild alteration characterized only by increased intraepithelial lymphocytes (Marsh type 1 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia (Marsh type 3 lesion) ([figure 1](#) and [picture 1](#)) [[11,19-23](#)]. The Marsh type 4 lesion has the same histologic features seen in the type 3 lesion except that the crypts are hypoplastic.

Failure to improve on a gluten-free diet is usually due to poor dietary compliance or other underlying malabsorptive disorders. However, in rare cases, diet-refractory celiac disease may be related to sprue-associated lymphoma or to collagenous sprue, a related but little-understood disorder. (See ["Management of celiac disease in adults", section on 'Refractory sprue'](#).)

**Atypical disease** — In some patients, the extraintestinal manifestations are predominant, and there are few or no gastrointestinal symptoms. As for patients with classical disease, the diagnosis requires serologic testing, biopsy evidence of villous atrophy, and improvement of symptoms on a gluten-free diet.

**Silent/subclinical celiac disease** — These patients have no discernable symptoms of celiac disease, but have a positive specific serologic test for celiac disease and biopsy evidence of villous atrophy. These cases are usually detected by screening of high-risk groups. The term "silent" may be a misnomer; after treatment with a gluten-free diet, many of these patients retrospectively recognize symptoms that they had not previously considered to be abnormal. (See ["Subclinical disease"](#) below.)

**Latent/potential disease** — Individuals with celiac disease, but who have normal jejunal mucosa and no or minor symptoms at least at one time point while on a normal, gluten-containing diet, are said to have "latent" celiac disease [[23](#)]. Two variants of latent celiac disease have been identified:

- Celiac disease was present before, usually in childhood; the patient recovered completely with a gluten-free diet, remaining "silent" even when a normal diet is adopted.
- A normal mucosa was diagnosed at an earlier occasion while ingesting a normal diet, but celiac disease developed later.

Patients who have never had a biopsy consistent with celiac disease but show immunologic abnormalities characteristic for the disorder (eg, positive IgA to endomysium, a "celiac intestinal antibody pattern," and increased intraepithelial lymphocytes) are said to have "potential" celiac disease [24]. These patients often have a genetic predisposition, especially HLA-DQ2, and a first-degree relative with celiac disease [21]. (See '[High-risk groups](#)' below.)

## EPIDEMIOLOGY

**General population** — Celiac disease occurs primarily in Caucasians. In Europe and the United States, prevalence estimates range from 1:80 to 1:300 children (3 to 13 per 1000 children) [1].

Prevalence estimates have increased with the advent of highly sensitive and specific screening tests, which identified many patients with minimal or no symptoms. Epidemiological studies using these tests with biopsy verification established prevalences of 1:300 to 1:500 in most countries [25]. A large screening study in the United States suggested a prevalence of 1:133 among patients with no risk factors or symptoms [26]. These estimates are similar to those found in European studies [27-30].

Even those not ethnically derived from European populations can develop celiac disease if they have an appropriate genetic background. Punjabis from India living in England and eating a gluten-rich diet developed this disorder 2.9 times more often than Europeans [31]. A disorder named "summer diarrhea" had long been known in their indigenous country, when wheat replaced maize during the summer season. Furthermore, a very high prevalence rate of 5 percent was documented for the Saharawi population of Northern Africa [32]. It is also common in Egypt [33], Tunisia [34], and other populations in North Africa, the Middle East, and Southern Asia [35]. The prevalence in some developing countries is probably underestimated due to limited access to diagnostic facilities and confounding of the disease with other causes of small intestinal damage. Overall, the global distribution of the disease seems to parallel the distribution of HLA genotypes that predispose to celiac disease, provided that the population is also exposed to gluten [36].

One of the largest screening investigations of celiac disease was performed in 17,201 school children, aged 6 to 15 years, who were recruited from several regions of Italy and represented 69 percent of the eligible population [37]. The prevalence was 1:184 and the ratio of asymptomatic to symptomatic cases was a remarkable 7:1 ([table 1](#)). Based upon these data, it was estimated that the number of affected persons in Italy alone was 220,000, three-quarters of whom were unidentified [38].

These findings indicate that the number of so-called silent celiacs (a misnomer

because most of these patients suffer from nonspecific symptoms) is much higher than the number of patients with classic celiac disease.

**High-risk groups** — The prevalence of celiac disease as detected by screening programs using specific antibodies is substantially increased in the following groups as compared to the general population ([table 2](#)):

- First- and second-degree relatives of patients with celiac disease [[1,26](#)]
- Down syndrome [[1,39](#)]
- Type 1 diabetes [[40-42](#)]
- IgA deficiency [[1,43](#)]
- Turner syndrome [[44](#)]
- Williams syndrome [[45](#)]
- Autoimmune thyroiditis [[1,46,47](#)]

Individuals with Down syndrome appear to have the highest risk, as up to 16 percent are affected (a 20-fold increase in risk over the general population). For the other groups, between 2 and 7 percent are affected, representing a 3- to 10-fold increase in risk as compared to the general population [[1,26,40-42,44,45](#)]. For autoimmune thyroiditis, the association is weak during childhood and appears to increase with age [[1](#)].

Evidence for these associations is discussed in detail separately. (See '[Diabetes mellitus](#)' below and '[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)', section on 'Associated conditions'.)

**SYMPTOMS** — Although originally recognized largely as a disease of infants, celiac disease most often presents later, between the ages of 10 and 40. Thus, the classical description of a child with life-threatening malabsorption often is replaced by atypical presentation of celiac disease in older children or adults. This changing presentation of the disease may be due to longer periods of breast-feeding and the later introduction of gluten into the infant diet, and increasing recognition of subclinical disease due to advances in serological screening [[48](#)].

**Gastrointestinal symptoms** — Classically, celiac disease presented between 6 and 24 months of age, after the introduction of gluten into the diet [[1](#)]. The children have chronic diarrhea, anorexia, abdominal distension and pain, and failure to thrive or weight loss; some may also have vomiting. If the diagnosis is delayed, children may present with signs of severe malnutrition. Severely affected infants may present with a celiac crisis and the hemodynamic and metabolic consequences of dehydration.

Gastrointestinal symptoms in older children and adults are similar, but usually less dramatic. Paradoxically, the disease may cause either constipation or diarrhea. When diarrhea is present, the stools are often bulky and foul-smelling, and may

float because of steatorrhea. Flatulence and abdominal distension (caused by colonic bacterial digestion of malabsorbed nutrients) are common. These symptoms may be accompanied by the consequences of malabsorption, such as growth failure, weight loss, severe anemia, neurologic disorders from deficiencies of B vitamins, and osteopenia from deficiency of vitamin D and calcium.

**Nongastrointestinal manifestations** — Numerous nongastrointestinal manifestations of celiac disease have been described ([table 3](#)). Conditions associated with celiac disease in adults are described in detail separately [[49](#)]. In many patients, nongastrointestinal symptoms are the presenting complaint and should prompt the consideration of serologic testing. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)" and "[Diagnosis of celiac disease](#)".)

**Growth and development** — Between 8 and 10 percent of children with apparent "idiopathic" short stature have serologic evidence of celiac disease [[1](#)]. Patients with gastrointestinal symptoms have slightly attenuated adult height unless treated prior to puberty [[50](#)]. Delay in linear growth may occur even when weight for height is relatively normal, and in the absence of significant gastrointestinal symptoms. Thus, the process is probably not entirely attributable to undernutrition.

Boys with untreated celiac disease have reduced levels of serum dihydrotestosterone in a pattern suggesting androgen resistance [[1,51](#)]. Adolescent girls may have an increased frequency of menstrual abnormalities such as delayed menarche, and later may have problems with infertility and experience an early menopause [[51-55](#)]. Treatment with a gluten-free diet appears to prevent these problems. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Menstrual and reproductive issues'.)

**Neurologic disease and behavioral symptoms** — Celiac disease may have as its primary manifestation neurologic or behavioral symptoms. Several reports in adults have described an association between celiac disease and neuropsychiatric symptoms such as ataxia, peripheral neuropathy, depression, anxiety, or epilepsy [[56-62](#)]. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Neuropsychiatric disease'.)

In children with celiac disease, clinically apparent neurologic disorders are uncommon, and the evidence supporting the association with celiac disease is weak. Disorders that may be associated with celiac disease include hypotonia, developmental delay, learning disorders and ADHD, headache, and cerebellar ataxia [[63,64](#)]. Epileptic disorders are only slightly more common among children with celiac disease, and there is no increase in the frequency of tic disorders. A population-based study in Italy found that clinically diagnosed neurologic or



psychiatric disorders among children with celiac disease was only slightly increased as compared to healthy controls [65]. In the same report, children with known or cryptogenic neurologic disorders did not have a higher prevalence of celiac disease as compared to the general population. Similarly, celiac disease was not overrepresented in a population of adolescent psychiatric outpatients in Finland [66], but depression and disruptive behavioral disorders were nonetheless more common among children with celiac disease than in matched controls [67].

Although clinically apparent neurologic disorders are unusual in children with celiac disease, subclinical neurologic abnormalities are common, and may affect the central and peripheral nervous systems. In a study of children with newly diagnosed celiac disease, almost 20 percent had subclinical neurologic abnormalities [68]. Among 27 children, two had peripheral polyneuropathy documented with electromyography, one had prolonged latencies in somatosensory evoked potential, and two had MRI abnormalities consisting of pontine demyelination or cortical atrophy. Similarly, there is some evidence of regional hypoperfusion of the cerebrum in adult patients with untreated celiac disease [66]. In most, but not all such conditions, improvement is observed after treatment with a gluten-free diet [61,63,69,70].

The pathogenesis of the neurologic symptoms is unclear. Some of the disorders, such as infantile hypotonia and developmental delay, may be caused by malnutrition, including specific micronutrient deficiencies; these problems tend to resolve on a gluten-free diet. However, there is increasing evidence that some or all of these neurologic abnormalities are caused by autoimmune mechanisms. As an example, widespread IgA tissue transglutaminase deposition around vessels in the cerebellum has been described [71]. In particular, anti-ganglioside antibodies may be involved in the pathogenesis of neurologic symptoms [72], although studies examining this possibility have had somewhat conflicting results. These findings suggest that an immune-mediated process may lead to gluten ataxia and/or peripheral neuropathy [71].

**Dermatitis herpetiformis** — There are a number of skin manifestations of celiac disease. Dermatitis herpetiformis is the most common (table 4), occurring in up to 24 percent of adult patients with celiac disease [73,74]. A few reports have suggested an association between psoriasis and elevated levels of antibodies to gliadin, reticulin, or tissue transglutaminase, but a strong association between psoriasis and celiac disease has not been documented [75,76].

Approximately 85 percent of adult patients with dermatitis herpetiformis have the characteristic changes of celiac disease on intestinal biopsy, although the majority have no gastrointestinal symptoms. Dermatitis herpetiformis is less common prior to puberty, but has been reported in patients as young as 8 months old [77,78]. It



is commonly misdiagnosed as atopic dermatitis, scabies, or linear IgA dermatosis [79].

Dermatitis herpetiformis is characterized by an itchy papular vesicular eruption usually located symmetrically on the extensor surfaces of the elbows, knees, buttocks, sacrum, face, neck, trunk, and occasionally within the mouth (picture 2A-B). The predominant symptoms are itching and burning that are rapidly relieved with rupture of the blisters.

The earliest abnormality comprises a small erythematous macule 2 to 3 mm in diameter that quickly develops into a papule. Small vesicles then appear to coalesce. Scratching causes them to rupture, dry up, and leave an area of pigmentation and scarring. The diagnosis can be confirmed by the demonstration of granular IgA deposition in an area of the skin not affected by blistering, along the subepidermal membrane. The results of the skin biopsy are sufficient to make the diagnosis of dermatitis herpetiformis. Many experts recommend a lifelong gluten-free diet based on the results of the skin biopsy alone, and an intestinal biopsy is not required.

Similar to celiac disease, anti-tTG antibodies are elevated in patients with dermatitis herpetiformis, confirming the pathogenetic relation of the diseases [80]. Although patients with dermatitis herpetiformis may have a symptomatic response to medications such as dapsone, complete resolution of the skin lesions in most patients will not occur without gluten withdrawal [81]. (See "[Management of celiac disease in children](#)", section on 'Dermatitis herpetiformis'.)

**Dental enamel defects** — Dental enamel defects involving the secondary dentition are more common among children and adults with celiac disease, and may occur in the absence of gastrointestinal symptoms [82]. The enamel defects considered to be specific to celiac disease are symmetrically distributed and detectable in all four quadrants of the dentition [83]. Defects may consist of cream, yellow, or brown opacities, loss of enamel glaze, horizontal grooves, or shallow pits (picture 3). The incisors are most commonly affected. The prevalence of enamel defects in children with celiac disease varies from 38 to 96 percent, as compared to 0.6 to 17 percent in control subjects [83,84]. There is some evidence that these defects are mediated by immunologic mechanisms (associated with the HLA allele DR3), and not by malabsorption of nutrients such as calcium [85]. Early identification and treatment of celiac disease may prevent the development of the enamel defects [86].

**Metabolic bone disease** — Bone loss (usually osteomalacia) occurs commonly in celiac disease and can occur in patients without gastrointestinal symptoms [87-90]. These patients have secondary hyperparathyroidism that probably is caused by vitamin D deficiency [91,92].

In children, metabolic bone disease generally resolves with a gluten-free diet [92-94]. In a study of 30 children and adolescents maintained on a long-term gluten-free diet (average 10.7 years), bone mineral density and serum markers of bone metabolism completely normalized [94].

In adults, metabolic bone disease generally improves on a gluten-free diet, including in those with clinically silent celiac disease. However, the abnormalities may not resolve entirely [89,91]. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Metabolic bone disease'.) The American Gastroenterological Association (AGA) guideline for osteoporosis in gastrointestinal diseases [95], as well as other AGA guidelines, can be accessed through the AGA Web site at [www.gastro.org/practice/medical-position-statements](http://www.gastro.org/practice/medical-position-statements).

**Arthritis** — About 25 percent of adults with celiac disease have arthritis [96]. In children, celiac disease is reported in 2 to 3 percent of those presenting with juvenile idiopathic arthritis or juvenile chronic arthritis [97,98].

**Liver disease** — Mild elevations in serum aminotransferases (AST and ALT) were seen in 42 percent of adult patients with celiac disease [99]. Conversely, celiac disease is found in 5 to 10 percent of adults with chronic elevations of aminotransferases [100]. Studies of children with celiac disease suggest that aminotransferase elevations are also common at diagnosis (32 to 54 percent), particularly in patients presenting with the classical symptoms of the disease [101,102]. In most patients the aminotransferases normalize with a gluten-free diet.

Patients with celiac disease also appear to have increased risks for a broad spectrum of liver diseases, including acute hepatitis, primary biliary cirrhosis, and chronic hepatitis including autoimmune hepatitis [103-105]. Several cases of severe liver disease with cirrhosis in children with celiac disease have been reported [106], but celiac disease is not established as a causative factor.

**Iron deficiency** — Celiac disease is a frequent cause of iron deficiency anemia in adults [107,108]. Consequently, iron deficiency anemia is an indication for celiac screening in adults. Although anemia is common among children with celiac disease, there is not good evidence that the prevalence of celiac disease is significantly increased among children with iron deficiency anemia [1].

**Subclinical disease** — The development and widespread availability of serologic screening has led to the understanding that celiac disease can exist in a very mild form and may go largely undetected because most patients have mild and nonspecific symptoms, such as fatigue, borderline iron deficiency, or otherwise unexplained elevations in serum aminotransferases [109,110], or no symptoms at all [90]. Sometimes the child's only overt problem may be short stature.

Monosymptomatic forms of celiac disease have been reported such as severe constipation, anemia, dental enamel hypoplasia [111], delayed puberty, and sterility in women [112]. The most common type of anemia in celiac disease is caused by iron deficiency; megaloblastic anemia is rare. Serum iron, serum folate, and red cell folate are usually all reduced in patients older than 1 year. (See '[Iron deficiency](#)' above.)

The range of symptoms in children with subclinical disease is illustrated by a study of children whose celiac disease was diagnosed through a screening program [37]. Most of these children had minimal gastrointestinal symptoms. However, there were numerous important clinical and laboratory findings, such as iron deficiency, recurrent abdominal pain, and mood changes ([table 5](#)). In another study, 31 percent of patients with subclinical disease (versus 67 percent with classic symptoms) were malnourished [113]. Once on a gluten-free diet, all reported objective and subjective improvement of well-being, as they recognized symptoms they had not previously considered to be abnormal.

Even in individuals with minimal symptoms, establishing and treating subclinical celiac disease may help to identify and treat unsuspected nutritional deficiencies, and to reduce the risk of low-birth-weight infants born to affected mothers. It is less clear whether these individuals have increased risk for malignancies or autoimmune diseases that might be reduced by treatment with a gluten-free diet.

**Risk of malignancy** — Several reports have suggested increased risk for some malignancies, particularly non-Hodgkin lymphoma and gastrointestinal cancers, in adults with celiac disease compared to the general population. The incidence of cancers does not appear to be increased during childhood or adolescence.

At least one study suggests that the risk for malignancy is reduced by long-term treatment with a gluten-free diet [114]. Although this has not been fully established, it is one of the rationales for recommending lifelong treatment for all patients with celiac disease, even for those with minimal gastrointestinal symptoms. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on '[Risk of malignancy and mortality](#)'.)

**ASSOCIATED CONDITIONS** — Celiac disease frequently is associated with Down syndrome, Williams syndrome, Turner syndrome, selective IgA deficiency, and several autoimmune conditions such as type 1 diabetes mellitus, and thyroid disease ([table 2](#)).

**Diabetes mellitus** — Celiac disease is associated closely with type 1 diabetes mellitus [115-118]. In several reports, between 2.6 and 7.8 percent of adults with type 1 diabetes had IgA autoantibodies to endomysium or to tissue transglutaminase; most such patients were proven to have celiac disease with

small bowel biopsy [74,119]. Many such patients had no overt clinical manifestations of celiac disease [74]. Other reports have demonstrated that as many as 3.5 percent of children of parents with type 1 diabetes have celiac disease, the prevalence of which increases with age [41].

A causal relationship between celiac disease and diabetes mellitus has been suggested, but not established. A few studies in humans [120] and animals [121,122] suggest that celiac disease may trigger autoimmune processes leading to diabetes. One study noted that the prevalence of autoimmune diseases, including Type 1 diabetes mellitus, may be related to the duration of exposure to gluten, and may reach more than 30 percent in patients diagnosed with celiac disease after age 20 [123]. However, other observations suggest that celiac disease does not trigger diabetes: the age of onset and the severity of diabetes do not appear to be influenced by the presence of celiac disease [74] and celiac autoantibodies usually develop after the onset of diabetes [124]. Thus, larger and prospective clinical studies are required to clarify the relationship between celiac disease, type 1 diabetes, and other autoimmune disorders.

Whether a gluten-free diet improves diabetes in diabetic patients with celiac disease is unclear. Only two small studies, one retrospective [125] and one short-term [116], investigated the effect of a strict gluten-free diet on type 1 diabetics with silent celiac disease. Patients showed at best a trend toward an increased body mass index, but no change in folate or hemoglobin levels or insulin requirements. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Diabetes mellitus'.)

**Autoimmune thyroiditis** — About 10 percent of individuals with autoimmune thyroiditis develop celiac disease [47]. Conversely, about 10 percent of individuals with celiac disease have autoimmune thyroiditis, and its clinical course does not appear to be affected by a gluten-free diet [47]. (See "[Acquired hypothyroidism in childhood and adolescence](#)", section on 'Chronic autoimmune thyroiditis'.)

Despite this association, the presence of antithyroid antibodies at diagnosis has a low predictive value for the development of thyroid hypofunction. In a series of 135 children with celiac disease, 12 percent had positive antithyroid antibody titers at diagnosis [126]. Approximately 12 percent of the patients had elevated thyroid stimulating hormone levels, suggesting subclinical hypothyroidism, regardless of whether the antithyroid antibody titers were positive. In most of these patients, the subclinical hypothyroidism normalized during the follow up period ( $8.9 \pm 4$  years on a gluten-free diet). Among patients with persistently positive antithyroid antibodies during the follow up period, subclinical hypothyroidism developed in 25 percent. Thus, this study does not suggest that treatment with a gluten-free diet alters the clinical course of autoimmune thyroiditis in patients with celiac disease.

**Other** — Celiac disease occurs in up to 16 percent of individuals with Down syndrome [39] and up to 10 percent of individuals with selective IgA deficiency [43]; the prevalence of celiac disease is also increased in Williams and Turner syndromes [1].

Weaker associations with primary biliary cirrhosis, as well as a variety of other liver diseases, have been described in adults. Evidence for these associations is described separately. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)", section on 'Associated conditions'.)

**DIAGNOSIS** — The steps to establishing a diagnosis of celiac disease are summarized here, and discussed in detail separately. The following guidelines are recommended by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition [1]. (See "[Diagnosis of celiac disease](#)".)

**Diagnostic approach** — The diagnosis of celiac disease typically requires both of the following:

- The presence of characteristic histologic changes on small intestinal biopsy in a symptomatic individual.
- Complete symptom resolution on a gluten free diet.

Serological tests that revert from positive to negative on a gluten-free diet may be used as supportive evidence of the diagnosis, and are particularly valuable in individuals with minimal symptoms.

The diagnosis is presumptively established when there is concordance between the serologic results and the biopsy findings. It is confirmed when symptoms resolve subsequently on a gluten-free diet. Demonstration of histologic normalization is no longer required.

**Whom to test** — The benefit of screening for asymptomatic celiac disease has not yet been established by evidence-based criteria. Such a strategy could possibly result in recognition and correction of subclinical nutritional deficiency states, resolution of mild symptoms, and potentially decrease the risk for malignancy. However, there are few data to support these beneficial effects and the strategy would require many asymptomatic individuals to adhere to a difficult dietary regimen.

We agree with the NASPGHAN and international recommendations that serologic screening for celiac disease be performed in the following groups of children, provided they are on a gluten-containing diet [[1,35](#)].

Patients with the following clinical signs and symptoms, if not otherwise explained:

- Failure to thrive
- Persistent diarrhea
- Chronic constipation, recurrent abdominal pain, or vomiting
- Dental enamel hypoplasia of permanent teeth (symmetric distribution)
- Idiopathic short stature
- Significant pubertal delay
- Iron deficiency anemia not responsive to supplementation

All members of the following high-risk groups:

- First-degree relatives of patients with celiac disease
- Autoimmune thyroiditis
- Type 1 diabetes
- Down syndrome
- Turner syndrome
- Williams syndrome
- Selective IgA deficiency

In suggesting screening for asymptomatic individuals in these high-risk groups, these guidelines differ from those used for adults in the United States [[4](#)]. This difference in recommendations reflects a debate about the utility of screening for celiac disease among truly asymptomatic individuals belonging to a high-risk group, because the benefit of treating such individuals has not been proven. Guidelines from the United Kingdom encourage testing for the first three of these high-risk groups, and suggest consideration of testing for the other groups on this list, as well as for individuals with a variety of nonspecific symptoms [[127](#)]. (See "[Diagnosis of celiac disease](#)", section on 'Who should be tested'.)

The debate continues about whether asymptomatic individuals in these high-risk groups should be screened, and recommendations may change as new information arises about the potential risks and benefits of screening. As an example, a study of a celiac screening program for children with type 1 diabetes mellitus compared clinical characteristics of 71 children with asymptomatic celiac disease with matched controls [[128](#)]. The children with celiac disease were slightly thinner (as indicated by a lower body mass index z-score), but height, bone mineral density and diabetes control were similar. Thus, it is reasonable to question the need for celiac screening and the added burden of a gluten-free diet for patients with type 1 diabetes and no symptoms of celiac disease, and to make treatment decisions on a

case-by-case basis, based on a discussion of estimated risks, symptoms, and treatment burden. (See ["Associated autoimmune diseases in children and adolescents with type 1 diabetes mellitus".](#))

If screening is undertaken for asymptomatic individuals in these high-risk groups, testing should be performed at three years of age or older and on a gluten-containing diet for at least one year. If initial results are negative, screening tests should be repeated at intervals, or if symptoms develop. The optimal time interval for subsequent screening has not been studied, but in our practice, we screen asymptomatic members of these groups every three to five years during childhood.

Patients with dermatitis herpetiformis established by skin biopsy are presumed to have celiac disease and treated without other diagnostic studies. A baseline measurement of tTG-antibodies is valuable to monitor improvement after institution of a gluten free diet.

**How to test** — Serologic tests for celiac disease are useful for screening and are an important step in the diagnosis of the disease ([table 6](#)). Currently, the most valuable test is for antibodies against tissue transglutaminase (anti-tTG), which is highly sensitive, specific, and more cost-effective than other antibody tests. The diagnostic accuracy of IgA anti-tTG immunoassays has been optimized by the use of human tTG in place of the non-human tTG preparations used in earlier immunoassay kits. Using second-generation ELISA technology, the sensitivity and specificity of anti-tTG antibodies for biopsy-proven celiac disease are generally above 96 percent [[1,129,130](#)]. Sensitivities are somewhat lower in children younger than two years [[131](#)].

Immunofluorescence test for IgA antibodies to endomysium, a structure of the smooth muscle connective tissue, is also highly sensitive and specific [[27](#)]. However, this test is generally more expensive than anti-tTG, and its accuracy is more dependent on interpretation by laboratory personnel. Tests measuring IgG and IgA antibodies to gliadin are considerably less reliable [[132](#)], although a second generation anti-gliadin antibody test (Deamidated Gliadin Peptide (DGP)) yields far higher diagnostic accuracy [[133](#)]. Tests of antireticulin antibodies have reasonably high specificity, but lower sensitivity, and are no longer commonly used [[134](#)]. (See ["Diagnosis of celiac disease", section on 'Serologic evaluation'.](#))

For most patients, we recommend measuring IgA antibodies to human recombinant tissue transglutaminase (tTG). This test is highly specific and sensitive, although false-positive and false-negative results may still occur with some frequency in populations with a low risk for celiac disease. Measurement of IgA antibodies to endomysium are equally accurate, but more expensive and somewhat dependent on interpretation error. (See ['Autoimmunity'](#) above and ["Diagnosis of celiac disease".](#))



For individuals with known selective IgA deficiency, testing should be performed with IgG antibodies to tTG instead of the usual IgA-based antibody test. Approximately 2 percent of children with celiac disease will have previously unrecognized IgA deficiency. Therefore, total IgA should be measured in children with negative results of IgA-tTG but a high clinical suspicion of celiac disease.

All individuals with positive tTG antibodies or antiendomysial antibodies should have an intestinal biopsy to establish the diagnosis of celiac disease. The biopsy should be performed with the patient on a gluten-containing diet. Multiple biopsies should be taken from the distal duodenum and duodenal bulb and interpreted by an expert pathologist; the disease may have a patchy distribution [[135-137](#)]. (See ["Diagnosis of celiac disease", section on 'Diagnostic approach'](#).)

**Whom to treat** — Treatment with a gluten-free diet is recommended for both diagnostic and therapeutic purposes for all children in one of the following groups:

- Children with characteristic findings on intestinal biopsy and symptoms consistent with celiac disease (including nonspecific symptoms such as constipation or abdominal pain).
- Children with characteristic findings on intestinal biopsy and belonging to one of the above high-risk groups (eg, relatives of patients with established celiac disease, or patients with type 1 diabetes), whether or not there are associated symptoms.
- Patients with dermatitis herpetiformis confirmed by skin biopsy.

We do NOT recommend beginning a gluten-free diet prior to evaluating an intestinal biopsy, because the symptoms of celiac disease are nonspecific and the biopsy is essential to making the diagnosis.

Patients with positive tests for tissue transglutaminase or anti-endomysial antibodies, but normal results of small bowel biopsies, are considered to have latent or potential celiac disease. We suggest NOT treating such patients with a gluten-free diet if they do not have symptoms. However, it is important that the evaluation of such patients include expert review of multiple intestinal biopsies since the histologic abnormalities can be patchy. Furthermore, these patients should be carefully monitored for growth failure and other symptoms that might suggest active celiac disease, and should be rebiopsied if symptoms develop.

There is some evidence that symptomatic children with positive serologic tests for celiac disease, but apparently normal biopsies are very likely to have celiac disease: One report followed eight children with positive serologic tests (anti endomysial antibodies) and some gastrointestinal symptoms, but normal intestinal histology who continued to consume a gluten-containing diet. Within two years,

seven of these eight children had developed marked mucosal atrophy and were diagnosed with celiac disease [[138](#)]. Therefore, decisions about whether to begin a gluten-free diet for patients with positive serologic tests but normal biopsy results should be made on a case-by-case basis with the family, after consideration of the patient's level of symptoms, appropriate exclusion of other causes of the symptoms, the burden of maintaining a gluten-free diet, and the adequacy of the biopsied tissue samples.

Treatment of individuals with confirmed celiac disease consists of a lifelong gluten-free diet. Details of treatment and monitoring are discussed separately. (See "[Management of celiac disease in children](#)".)

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "[Patient information: Celiac disease in children](#)".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

## **SUMMARY AND RECOMMENDATIONS**

- Celiac disease is an immune-mediated inflammation of the small intestine caused by sensitivity to dietary gluten and related proteins in genetically sensitive individuals. The disorder is common, occurring in 0.5 to 1 percent of the general population in most countries. The grains that contain the triggering proteins are wheat, barley, and rye; there is some controversy as to whether oats also can cause the disease. The small intestinal mucosa improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. (See '[Introduction](#)' above.)
- Classic clinical features of patients with celiac disease include symptoms of malabsorption such as diarrhea, steatorrhea, weight loss, or other signs of nutrient or vitamin deficiency, the presence of characteristic histologic changes (including villous atrophy) on small intestinal biopsy, and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months. (See '[Classic disease](#)' above.)
- Some patients with celiac disease have extraintestinal manifestations, in addition to or instead of gastrointestinal symptoms. The most specific extraintestinal manifestation is dermatitis herpetiformis, which is uncommon prior to puberty ([picture 2A-B](#)). Other extraintestinal manifestations include delayed growth and pubertal development, neurologic disease and behavioral symptoms, arthritis, dental enamel defects, liver disease, and iron deficiency. (See '[Nongastrointestinal manifestations](#)' above.)
- It is now recognized that some patients with celiac disease have mild or

minimal symptoms, but positive celiac serologies. If these patients have abnormal intestinal biopsies they are said to have “silent” celiac disease, and if their biopsies are normal they are said to have “potential” celiac disease. Many of these patients will develop symptoms and/or worsening intestinal lesions if they continue on a gluten-containing diet. (See '[Silent/subclinical celiac disease](#)' above and '[Latent/potential disease](#)' above.)

- We suggest serologic screening for celiac disease in patients with failure to thrive, persistent diarrhea, chronic constipation, recurrent abdominal pain, dental enamel hypoplasia of permanent teeth, idiopathic short stature, significant pubertal delay, or iron deficiency anemia not responsive to supplementation. In addition, we suggest screening individuals with the following disorders which are associated with an increased risk for celiac disease: first-degree relatives of patients with celiac disease, autoimmune thyroiditis, type 1 diabetes, Down syndrome, Turner syndrome, Williams syndrome, and selective IgA deficiency. (See '[Whom to test](#)' above.)
- Serologic screening is performed by measuring one of several antibodies that are specific for celiac disease ([table 6](#)). Currently, the most clinically useful test is for antibodies against tissue transglutaminase (anti-tTG), which is highly sensitive, specific, and more cost-effective than other antibody tests. (See '[How to test](#)' above.)
- Patients with positive results of the serologic screen should undergo endoscopy, with biopsies from several areas of the duodenum including the duodenal bulb. The histologic features of celiac disease range from a mild alteration characterized only by increased intraepithelial lymphocytes (Marsh type 1 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis, and crypt hyperplasia (Marsh type 3 lesion) ([figure 1](#) and [picture 1](#)). (See '[Classic disease](#)' above and '[Diagnostic approach](#)' above.)
- Patients with positive results of the serologic screen and histologic changes consistent with celiac disease should be given the presumptive diagnosis of celiac disease, and should be treated with a gluten-free diet. (See '[Whom to treat](#)' above.)
- We do NOT recommend beginning a gluten-free diet prior to a full evaluation for celiac disease, including intestinal biopsy. This is because the symptoms of celiac disease are nonspecific, and an intestinal biopsy is essential to making the diagnosis. (See '[Whom to treat](#)' above.)
- Patients with positive results of the serologic screen but normal intestinal biopsies probably have latent celiac disease, and may not require treatment

with a gluten-free diet if they are asymptomatic. However, because most of these patients will go on to develop intestinal lesions and symptoms, they should be monitored closely, and treatment should be considered if they develop symptoms. In patients who have symptoms but a normal intestinal biopsy, it is also reasonable to consider treatment with a gluten-free diet, after exclusion of other conditions and careful consideration of the potential benefits and treatment burden with the family. (See ['Whom to treat'](#) above.)

- Patients treated with a gluten-free diet should be monitored for changes in symptoms (including growth parameters) and serologies. A decrease in symptoms and normalization of antibodies confirms the diagnosis of celiac disease. (See ['Diagnostic approach'](#) above.) Details of treatment and monitoring are discussed in a separate topic review. (See ["Management of celiac disease in children"](#).)

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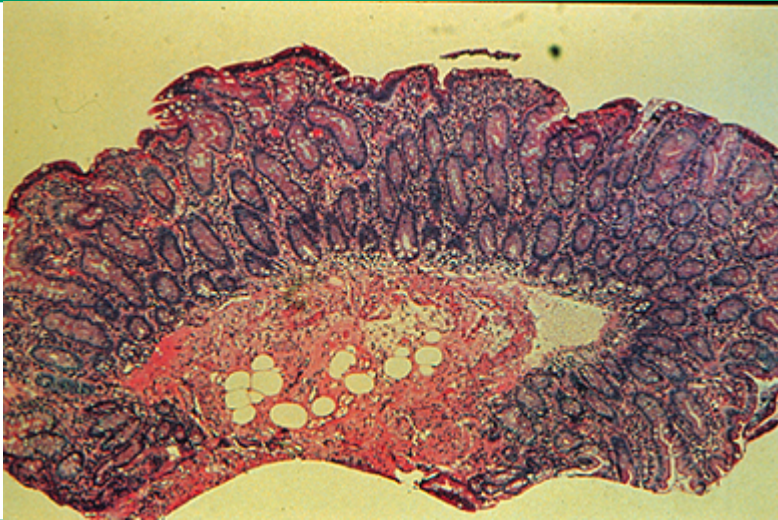
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## GRAPHICS

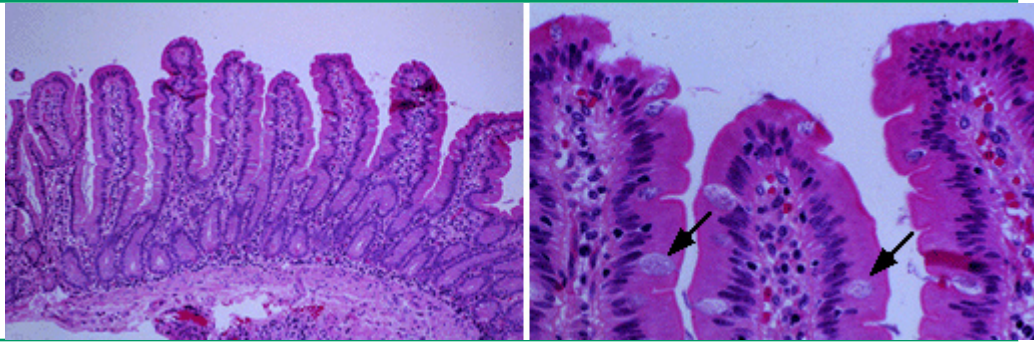
### Celiac disease



Low power view of a small bowel biopsy from a patient with celiac disease. The mucosa is flat with complete loss of the normal villous architecture. *Courtesy of Robert Odze, MD.*



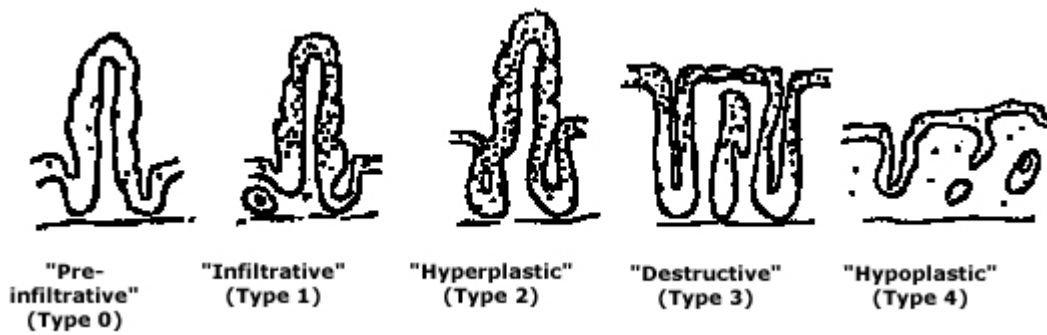
## Normal small intestine



Low (left) and high (right) power views of the normal villous architecture of the small intestine. The high power view shows the enterocytes and interspersed goblet cells (arrows). *Courtesy of Robert Odze, MD.*

## Intestinal lesions in celiac disease

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Schematic representation of the five main lesions associated with gluten sensitivity. The lesions range in histologic severity from a mild alteration characterized by increased intraepithelial lymphocytes (type 0 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis and crypt hyperplasia (type 3 lesion). The type 4 lesion is seen in T cell lymphoma. *Adapted from Marsh, MN, Gastroenterology 1992; 102:330.*

## Prevalence of celiac disease in 17,201 Italian school children (age 6 to 15)

Test	Percent positive
IgG and/or IgA antigliadin antibodies	7.50
IgA antigliadin and/or IgA endomysial antibodies	0.65
Intestinal biopsy performed	0.57
Villous atrophy seen on biopsy	0.44
Not biopsied but clinically celiac	0.04
Previously known celiac	0.06
<b>TOTAL with diagnosis of celiac disease</b>	<b>0.54</b>

*Adapted from: Catassi, C, Fabiani, E, Ratsch, IM, et al, Acta Pediatr 1996; 412(Suppl):29.*

## Prevalence of celiac disease in special populations

	Percent of group affected	Fold increase in risk as compared to general population
General population (US and Europe) <sup>[1]</sup>	0.7 to 1.0	-
Relatives of patient with celiac disease <sup>[1,2]</sup>		
first-degree relatives	4 to 5	6
second degree relatives	3	3
Down syndrome <sup>[2,3]</sup>	5 to 16	7 to 21
Type 1 diabetes <sup>[2,4]</sup>	5 to 10	7 to 13
IgA deficiency <sup>[2,5]</sup>	2 to 8	3 to 11
Williams syndrome <sup>[6]</sup>	8	11
Turner syndrome <sup>[2]</sup>	4 to 8	5 to 11
Autoimmune thyroid disease <sup>[7]</sup>	4.5	6 (less in children)

Data from:

1. Fasano, A, Berti, I, Gerarduzzi, T, et al. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: A large multicenter study. *Arch Intern Med* 2003; 163:286.
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## Nongastrointestinal manifestations of celiac disease in children

Skin
Dermatitis herpetiformis
Others (see table)
Growth and development
Short stature
Delayed puberty
Neuropsychiatric disease
Hypotonia
Developmental delay
Learning disorders
Headache
Cerebellar ataxia
Dental enamel defects
Metabolic bone disease
Arthritis
Liver disease
Iron deficiency

## Skin disorders associated with celiac disease

Acquired ichthyosis
Cutaneous amyloid
Cutaneous vasculitis
Dermatitis herpetiformis
Eczema
Epidermal necrolysis
Nodular prurigo
Pityriasis rubra pilaris
Pustular dermatitis



## Dermatitis herpetiformis

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A skin blister on the elbow of a subject with dermatitis herpetiformis. *Reproduced with permission from the American Gastroenterological Association. Ciclitira, PJ. Gastroenterology 2001; 120:1526.*

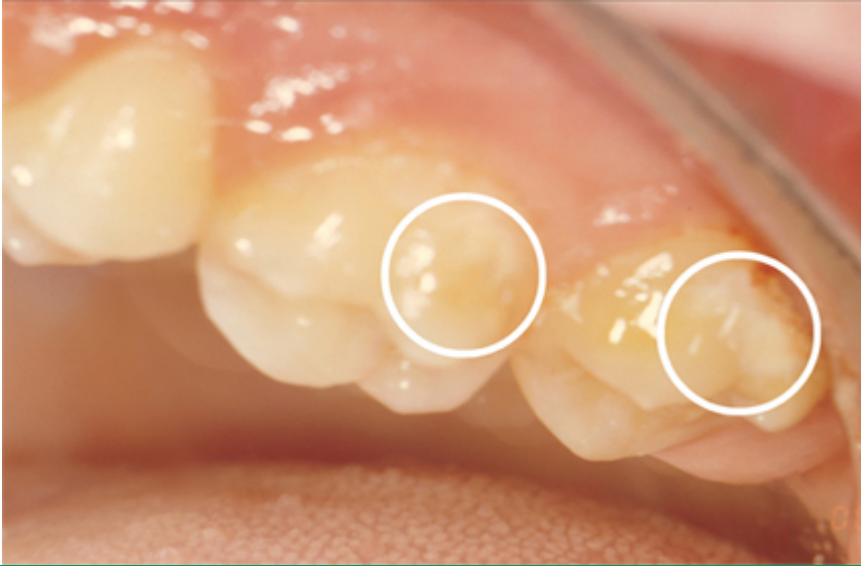
## Dermatitis herpetiformis



Herpetiform clusters of vesicles on an erythematous, edematous base with crusts and postinflammatory pigmentation on the upper back and shoulder. *Reproduced with permission from: Skin signs of immune, autoimmune, and rheumatic diseases. In: Color Atlas and Synopsis of Clinical Dermatology, 3rd ed, Fitzpatrick, TB, Johnson, RA, Wolff, K (Eds), McGraw-Hill, New York 1997. p.327. Copyright © 1997 McGraw Hill.*

## Dental celiac

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*Courtesy of Lisa Papagiannoulis, DDS, MS, School of Dental Medicine, University of Athens, Greece.*

## Clinical and laboratory findings in 82 oligosymptomatic Italian children with celiac disease detected by screening

Symptom	Percent
Iron deficiency	
With anemia	29
Without anemia	27
Recurrent abdominal pain	24
Mood changes	17
Recurrent aphthous stomatitis	11
Poor appetite	10
Recurrent diarrhea	9
Short stature	7
Abdominal distention	5
Constipation	2
Pubertal delay	2
Hypoalbuminemia	2

Data from: Catassi, C, Fabiani, E, Räscher, IM, et al, *Acta Paediatr* 1996; 412(Suppl):29.

## Sensitivity and specificity of antibody tests for celiac disease in children

	<b>Sensitivity, (percent)</b>	<b>Specificity, (percent)</b>
Tissue transglutaminase (IgA, human)	90 to 100	95 to 100
Anti-endomysial antibody (IgA)	93 to 100	98 to 100
Antigliadin antibody IgA	52 to 100	72 to 100
Antigliadin antibody IgG	83 to 100	47 to 94

*Data from: Basso, D, Guariso, G, Fasolo, M, et al. A new indirect chemiluminescent immunoassay to measure anti-tissue transglutaminase antibodies. J Pediatr Gastroenterol Nutr 2006; 43:613.*

*Hill, ID. What are the sensitivity and specificity of serologic tests for celiac disease? Do sensitivity and specificity vary in different populations? Gastroenterology 2005; 128 (4 Suppl 1):S25.*





## Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults

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**INTRODUCTION** — Celiac disease (also called gluten-sensitive enteropathy and nontropical sprue) was first described by Samuel Gee in 1888 in a report entitled "On the Coeliac Affection", although a similar description of a chronic, malabsorptive disorder by Aretaeus from Cappadocchia (now Turkey) reaches as far back as the second century AD [1].

The cause of celiac disease was unexplained until the Dutch pediatrician Willem K Dicke recognized an association between the consumption of bread and cereals and relapsing diarrhea. This observation was corroborated when, during periods of food shortage in the Second World War, the symptoms of his patients improved once bread was replaced by unconventional, non-cereal containing foods; this finding confirmed the usefulness of earlier, empirical diets that used pure fruit, potatoes, banana, milk, or meat [1-3].

Since symptoms reoccurred when bread was reintroduced after the war, Dicke and van de Kamer initiated controlled experiments exposing children with celiac disease to defined diets and then determined fecal weight and fecal fat as a measure of malabsorption. Wheat, barley, rye, and (to a minor degree) oats triggered malabsorption, which could be reversed after exclusion of these "toxic" cereals from the diet [4]. Shortly after, the toxic agents were found to be present in gluten, the alcohol-soluble fraction of wheat protein [5].

The celiac lesion in the proximal small intestine was first described in 1954. The primary findings were mucosal inflammation, crypt hyperplasia, and villous atrophy (picture 1) [6]. With the development of peroral biopsy, it became apparent that celiac disease and adult nontropical sprue shared the same features and pathogenesis [7]. When unrecognized and untreated, celiac disease is associated with increased mortality. (See '[Risk of malignancy and mortality](#)' below.)



The epidemiology, pathogenesis, and clinical manifestations of celiac disease will be reviewed here. Its management and the use of antibodies for diagnosis are presented separately. (See "[Management of celiac disease in adults](#)" and "[Diagnosis of celiac disease](#)".) This topic is also discussed in an official position statement issued by the American Gastroenterological Association [8].

## **PATHOGENESIS**

**Genetic factors** — The frequent intrafamilial occurrence and the remarkably close association with the HLA-DQ2 and/or DQ8 gene loci provide the basis of our current understanding of celiac disease as an immune disorder that is triggered by an environmental agent (the gliadin component of gluten) in genetically predisposed individuals [9,10]. It has been estimated that the HLA contribution to the development of celiac disease among siblings is 36 percent [11]. Thus, another gene or genes at an HLA-unlinked locus must also participate [12-16]. A particular association was found with chromosome 15q26, which contains a type 1 diabetes susceptibility locus [13], and with chromosome 5q and possibly 11q [14].

HLA typing for DQ2 (DQA1\*05; DQB1\*02) and DQ8 (DQA1\*03; DQB1\*0302) may be useful in individuals with equivocal small bowel histologic findings since celiac disease is unlikely if neither is present [17]. Homozygosity for HLA DQ2 has been associated with an increased risk for celiac disease [18,19] and enteropathy-associated T-cell lymphoma [18].

Non-HLA locus genes conferring risk for celiac disease have also been identified [15,16] and an increasing number of non-HLA risk alleles has been associated with an increased risk of celiac disease [15].

A genome wide association study in large numbers of patients with celiac disease and matched controls from the United Kingdom, Italy, and Ireland identified a number of genes involved in controlling immune responses [20]. In addition, type 1 diabetes and celiac disease share common genetic risk regions (including HLA-DQ). However, the new polymorphisms, even when taken together, contribute only 3 to 4 percent to the genetic risk for celiac disease, as compared with 30 to 40 percent for HLA-DQ2 or -DQ8.

**Serum autoantibodies** — Serologic studies are now used to further confirm the diagnosis of celiac disease. These include the ELISA for IgA antibodies to gliadin and the immunofluorescence test for IgA antibodies to endomysium, a structure of the smooth muscle connective tissue, the presence of which is virtually pathognomonic for celiac disease ([table 1](#)) [21]. The target autoantigen contained within the endomysium was identified as tissue transglutaminase [22]. IgA-antibodies against endomysium and the endomysial autoantigen tissue transglutaminase are highly sensitive and specific [23-25]. Some studies also

revealed a high sensitivity and specificity for IgG antibodies against deamidated gluten peptides, almost reaching that of IgA anti-transglutaminase antibodies [26]. (See "[Diagnosis of celiac disease](#)".)

Widespread use of these serologic tests has allowed earlier diagnosis, large scale population screening and thereby an improved understanding of its epidemiology.

**Gliadin reactive T cells** — Tissue transglutaminase is a ubiquitous intracellular enzyme that is released by inflammatory and endothelial cells and fibroblasts in response to mechanical irritation or inflammation. Once it has been secreted, it crosslinks glutamine-rich proteins such as gluten proteins from wheat. However, it can also deaminate glutamine residues in gluten to [glutamic acid](#). Deamination produces a negative charge in gluten peptides that increases their binding to HLA-DQ2 and DQ8 thereby potentiating their capacity to stimulate T-cells [27-29].

Initial studies suggested that, in adult patients, the dominant epitope responsible for the T-cell response appeared to be a deamidated glutamine residue (Q65E) of alpha gliadin [30]. In contrast, younger patients appeared to have a less restricted T-cell response with reactivity to a diverse set of gliadin and glutenin peptides [31]. This suggested that there may be a broad group of different gluten peptides that activate celiac disease in children, while with advancing age the T-cell response narrows to only a few deamidated peptides. However, a later study suggests that there is a broader range of gliadin peptides recognized by T cells in adults [32].

A common feature is the recognition of epitopes in gliadins that are located in regions rich in proline residues. A 33 amino acid peptide (A-gliadin, peptide 56-89) that is particularly resistant to gastrointestinal peptidases has been identified [33]. One study demonstrated that this peptide can be completely degraded by enterocytes in controls but only partly in celiac patients [34]. Enterocytes from patients with celiac disease also showed only limited digestion of peptide 31-49 of A-gliadin, a peptide that is not recognized by HLA-DQ2/DQ8. The high stability against proteolysis or the incomplete degradation of these gliadin peptides favors them as important initiators of the inflammatory response and toxic effects [34].

**Innate immunity** — Innate responses to gliadin (in addition to activation of pathogenic T cells) are also involved in the immune response, and perhaps even necessary to trigger the gliadin specific (adaptive) T cell response in genetically predisposed individuals [35]. The innate immune system uses "pattern recognition" to provide an early response to stimuli such as RNA, DNA, lipopolysaccharide, or viral proteins in contrast to the adaptive immune system, which depends upon HLA-presentation, T-cell recognition and expansion. In celiac disease, certain cereal peptides apparently can initiate innate immune responses in macrophages, monocytes, dendritic cells, and intestinal epithelia via yet unknown receptors and mechanisms [35-41].

**Autoantibodies and intraepithelial lymphocytes** — The relative pathogenic importance of humoral versus the established role of cellular immunity in the pathogenesis of celiac disease is uncertain. In a cell culture system, autoantibodies to tissue transglutaminase blocked intestinal epithelial differentiation [28,42]. Tissue transglutaminase may support the bioactivation of transforming growth factor beta 1, which is required for epithelial differentiation, a process that is impaired in celiac disease. Some inhibitory effect of isolated autoantibodies on tissue transglutaminase activity was also demonstrated in vitro [43]. However, residual enzymatic activity appears to be sufficient for protein crosslinking and (gliadin) deamidation reactions [44]. Therefore, the mucosal tTG activity in celiac disease, which cannot be completely blocked by the locally produced autoantibodies, may have a role in the pathogenesis of celiac disease [27,45].

The number of intraepithelial lymphocytes, which mainly bear the unusual gamma-delta T cell receptor, is increased in patients with active, gluten-sensitive sprue compared with normal subjects, while patients with refractory sprue (which is of uncertain relationship to celiac disease) also have aberrant lymphocytes with restricted gene rearrangements. The intraepithelial T lymphocytes show increased expression of interferon gamma and IL-10 [46]. However, the pathogenetic role of these lymphocytes, compared with the lamina propria lymphocytes, is controversial [47], and several inflammatory conditions, such as enteric infections and drug and food allergies that are unrelated to celiac disease can cause intraepithelial lymphocytosis [48].

**Gliadin receptor** — Gliadin receptor(s) on intestinal epithelial cells may mediate the transport of gliadin peptides to the lamina propria where T cell activation occurs. Identification of the receptors could lead to non-dietary therapies of celiac disease by creating drugs that interfere with receptor function. A study found that CD71 (the transferrin receptor) was increased in patients with celiac disease and was also expressed at the apical pole of enterocytes, in contrast to its usual location at the basolateral pole of enterocytes [49]. CD71 colocalized with secretory IgA and seemed to be responsible for the apical to basal retrotransport of secretory IgA. The authors concluded gluten peptides that are bound to secretory IgA (ie, IgA anti-gliadin antibodies) may be protected from degradation by the enterocytes, leading to accumulation in the lamina propria where T cell stimulation occurs [49]. (See "[Clinical manifestations and diagnosis of celiac disease in children](#)".)

Another study showed the colocalization of gliadin with the chemokine receptor

CXCR3 [50]. CXCR3 is usually expressed on T cells where it mediates their recruitment to sites of inflammation. Somewhat unexpectedly, CXCR3 was found on enterocytes, and increased levels were detected in intestinal tissue of patients with active celiac disease. The increased levels returned to baseline after introduction of a gluten-free diet. In cell lines, binding of gliadin to CXCR3 was followed by the recruitment of MyD88, which led to enhanced intestinal permeability.

Several questions remain unanswered and final proof of a central and specific gliadin (gluten) receptor on intestinal epithelial cells remains to be established.

**EPIDEMIOLOGY** — Celiac disease occurs primarily in whites of northern European ancestry. Reports in the 1950s suggested that the prevalence of celiac disease among Europeans ranged between 1:4000 and 1:8000. However, this diagnosis was based upon a clinical presentation with classic symptoms of malabsorption. The picture changed in the 1970s with rising awareness of the often oligosymptomatic form of celiac disease and the advent of sensitive and specific serologic assays for IgA antibodies to gliadin and endomysium. Epidemiological studies using these tests with biopsy verification established higher prevalences of 1:300 to 1:500 in most countries [51]. Studies in 2000 American blood donors, for example, suggest a prevalence of 1:250 based upon endomysial antibody testing [52]. In a report from Denmark, screening assays increased the prevalence from 1:10,000 to 1:300 [53].

These findings indicate that the number of so-called silent celiacs (a misnomer, since most of these patients suffer from nonspecific symptoms) is much higher than the number of patients with classic celiac disease.

**Prevalence** — The benefit of screening for asymptomatic celiac disease has not yet been established. Screening could result in the recognition and treatment of unrecognized nutritional deficiency states, resolution of mild symptoms, and a potential reduction in the risk for malignancy. However, these benefits require compliance of asymptomatic patients with a difficult dietary regimen which can reduce quality of life.

Screening programs based upon antibody testing have demonstrated a high prevalence of celiac disease [21,22,54-59]. In a screening study of 4615 adults from northern Italy, for example, IgA endomysial antibodies had a positive predictive value of 100 percent; comparable values for IgG and IgA antigliadin antibodies were only 2 and 12 percent, respectively, because of their lower specificity [21]. (See "[Diagnosis of celiac disease](#)".)

Population-based studies have suggested that recognized cases of celiac disease may only represent the tip of the celiac iceberg. One of the largest screening investigations of celiac disease was performed in 17,201 school children, aged 6 to

15 years, who were recruited from several regions of Italy and represented 69 percent of the eligible population [54]. The prevalence was 1:184 and the ratio of undiagnosed to diagnosed celiac disease was a remarkable 7:1 (table 2); most children had minor but significant nonspecific symptoms. Based upon these data, it was estimated that the number of affected persons in Italy alone was 220,000, three-quarters of whom were unidentified and only about 5 percent of whom were in an organized celiac society [60].

Screening investigation of 1,823 participants of the Belfast MONICA project for coronary risk factors detected 10 biopsy-proven new celiacs between 36 and 61 years of age, most of whom had iron or folate deficiency or nonspecific intestinal symptoms [61]. Together with the two known cases, the prevalence was 1:152. A similar prevalence (1:256) was noted in a screening study of 1866 Swedish blood donors [55] and even higher prevalences (1:99 and 1:96, respectively) were observed in studies of 3654 Finnish students and 3188 Italian school children [22,56].

Studies describe an increasing prevalence of celiac disease with age. An Italian survey documented that approximately 15 percent of newly diagnosed patients are older than 65 years and these patients very often suffer from symptoms for  $11 \pm 19$  years prior to correct diagnosis [62]. A study from Finland showed a prevalence of biopsy proven celiac disease of 2 percent for individuals aged between 52 and 74 [63].

One of the largest studies in the United States included 13,145 subjects (4508 first-degree relatives of patients with celiac disease, 1275 second-degree relatives, 3236 symptomatic patients, and 4126 not-at-risk individuals) who underwent screening [57]. In the at-risk groups, the prevalence of celiac disease was 1:22 in first-degree relatives, 1:39 in second-degree relatives, 1:56 in symptomatic patients, and 1:133 in the not-at-risk groups. These estimates are similar to those found in the European studies described above.

Even those not ethnically derived from European populations can develop celiac disease if they have an appropriate genetic background. Punjabis and Gujaratis from India who lived in England developed this disorder 2.7 times as often as Europeans when on a gluten-rich diet. A disorder named "summer diarrhea" had long been known in their indigenous country, when wheat replaced maize during the summer season [58].

In a screening study of school children from Punjab, North India, the prevalence of biopsy-proven celiac disease was 1:310 [64]. However, this was likely an underestimation, as only children with signs or symptoms suggestive of possible celiac disease (eg, chronic diarrhea, pallor) or with a first degree relative with celiac disease were screened.

**CLASSIFICATION** — For many years, celiac sprue was defined by a set of classic standards for diagnosis. However, the combination of serologic, genetic, and histologic data has led to the identification of two other classes of celiac disease.

**Classic disease** — The classic definition of celiac disease or gluten-sensitive enteropathy includes the following three features: villous atrophy; symptoms of malabsorption such as steatorrhea, weight loss, or other signs of nutrient or vitamin deficiency [7]; and resolution of the mucosal lesions and symptoms upon withdrawal of gluten-containing foods, usually within a few weeks to months. Patients with classic disease present with diarrhea, weight loss, or malabsorption, and possess antibodies against gliadin and especially tissue transglutaminase.

The severity of histologic changes in the small bowel does not necessarily correlate with the severity of clinical symptoms. Although there is a gradient of decreasing severity from the proximal to the distal small intestine, correlating with the higher proximal concentration of dietary gluten, sampling error can occur due to spotty features of mucosal inflammation. The histologic severity ranges from a mild alteration characterized by increased intraepithelial lymphocytes (type 0 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis and crypt hyperplasia (type 3 lesion) ([figure 1](#) and [picture 1](#)) [7,65-69]. The type 4 lesion has the same histologic features seen in the type 3 lesion, except that lamina propria hyperplasia becomes hypoplasia. The type 4 lesion is characteristic of T cell lymphoma.

Failure to improve on a gluten-free diet is mostly due to poor dietary compliance or other underlying malabsorptive disorders. However, in rare cases diet-refractory celiac disease may be related to sprue-associated, enteropathy-associated T-cell lymphoma (EATL) or to collagenous sprue, a related but little understood disorder. As noted above, some patients with refractory disease have aberrant intraepithelial lymphocytes with restricted gene rearrangements; the relation of this finding to the resistance to gluten restriction is not known [47].

**Atypical celiac disease** — Patients with atypical disease exhibit only minor gastrointestinal complaints. They can display anemia, dental enamel defects, osteoporosis, arthritis, increased transaminases, neurological symptoms, or infertility. However, most of these patients show severe mucosal damage and possess the celiac specific antibody pattern.

**Asymptomatic (silent) celiac disease** — Patients are often recognized incidentally

based upon screenings for antibodies against gliadin or tissue transglutaminase. Although these patients very often display the characteristic architectural remodelling of the intestinal mucosa seen in celiac disease (ie, crypt hyperplasia and villous atrophy), they do not show clinical symptoms. Often minor symptoms (eg, fatigue) are only realized after introduction of a gluten free diet.

**Latent celiac disease** — There are some patients who have normal jejunal mucosa and minor symptoms or no symptoms at one or more time points while on a normal, gluten-containing diet [69]. Two variants of what has been called latent celiac disease have been identified:

- Celiac disease was present before, usually in childhood; the patient recovered completely with a gluten-free diet, remaining "silent" even when a normal diet was reintroduced. About 20 percent of such patients continue to have latent disease (asymptomatic with normal villous architecture) into adulthood, while the others re-develop variable degrees of villous atrophy [70]. Latency may be transient and thus regular follow up of such patients is warranted.
- A normal mucosa was diagnosed at an earlier occasion while ingesting a normal diet, but celiac disease developed later.

**CLINICAL MANIFESTATIONS** — Although classically a disease of infants, celiac disease now often presents later, between the ages of 10 and 40 years. Thus, the impressive clinical picture of a child with life-threatening malabsorption is often replaced by the mostly atypical presentation of adult celiac disease. This is in part due to longer periods of breast-feeding and the later introduction of gluten in the infant diet.

Patients may present with the classic signs, including diarrhea with bulky, foul-smelling, floating stools due to steatorrhea and flatulence . These symptoms are paralleled by the consequences of malabsorption, such as growth failure in children, weight loss, severe anemia, neurologic disorders from deficiencies of B vitamins, and osteopenia from deficiency of vitamin D and calcium. However, there is a shift from fewer patients presenting with classical celiac disease to more patients with atypical symptoms or an asymptomatic presentation [71].

Adult patients with undiagnosed celiac disease rarely present with profuse diarrhea and severe metabolic disturbances (celiac crisis) [72].

**Subclinical disease** — The development and widespread availability of serologic screening has led to the understanding that celiac disease can exist in a very mild form and may go largely undetected, since most patients have mild and unspecific symptoms, such as fatigue, borderline iron deficiency (see '[Iron deficiency](#)' below), or otherwise unexplained elevations in serum aminotransferases, or no symptoms



at all [73]. Some patients are identified because of the physician's increased awareness. Those without any specific complaints may be diagnosed during screening programs or during endoscopy performed for other reasons (picture 2). Thus, celiac disease may represent a continuum with variable degrees of severity. One study suggested that the severity of disease correlated with the concentration of tissue transglutaminase antibody levels, but this correlation is weak [74].

Establishing the diagnosis of subclinical celiac disease is of potential importance for four reasons: the danger of malignancy, the presence of unsuspected nutritional deficiencies, the association with low-birth weight infants in affected mothers, and the occurrence of autoimmune disorders. The risk of malignancy in patients with subclinical celiac disease is not known, although (as discussed above) it appears to be lower than in patients who present with malabsorption symptoms. However, once the disease is in remission with a gluten-free diet, the risk approaches that of the normal population [75]. Some studies have found that the prevalence of autoimmune diseases (eg, Type 1 diabetes mellitus, collagen vascular disease, autoimmune thyroiditis) is related to the duration of undetected celiac disease, and may reach more than 30 percent of patients diagnosed after age 20 years [76]. However, this is likely to be related to common genetic predispositions, and the relationship between the duration of gluten exposure and the risk of autoimmune disorders remains unsettled [77]. (See "[Management of celiac disease in adults](#)".)

Oligosymptomatic patients with celiac disease may have significant nutritional deficiencies. The 82 patients with celiac disease, mostly oligosymptomatic, detected by screening of the adolescent Italian population described above exhibited a number of important clinical and laboratory findings such as iron deficiency, recurrent abdominal pain, and mood changes (table 3) [54]. In another study, 31 percent of patients with subclinical disease (versus 67 percent with classic symptoms) were malnourished [78]. Once on a gluten-free diet, all reported objective and subjective improvement of well-being, realizing symptoms that they had not recognized before.

**Nongastrointestinal manifestations** — A number of nongastrointestinal manifestations of celiac disease have been described (table 4) [79]. In some patients, they are the presenting symptom and should prompt the consideration of serologic testing. (See "[Diagnosis of celiac disease](#)".)

**Neuropsychiatric disease** — Several reports have described an association between celiac disease and neuropsychiatric symptoms such as ataxia, depression, anxiety, or epilepsy [80-88]. However, the diagnosis of celiac disease was frequently based only upon anti-gliadin antibodies (which lack specificity for celiac disease) and not all studies have detected these associations, making the relationship to celiac disease unclear.

**Arthritis** — A higher prevalence of osteoarthritis has been described in celiac disease, but whether there is a causal relationship is unclear [89].

**Iron deficiency** — Celiac disease may be a surprisingly frequent cause of iron deficiency anemia. One study of 93 patients presenting for evaluation of iron deficiency anemia found 11 (12 percent) with small bowel biopsy findings compatible with celiac disease [90]. Some had other mucosal abnormalities, such as esophagitis and gastritis, which could have been taken as the cause of the anemia and delayed the discovery of celiac disease. Similar findings were noted in another report in which 6 percent of 85 patients with iron deficiency anemia had celiac disease [91]. The incidence was 20 percent in the subgroup of nonresponders to supplemental iron.

Some reports have suggested that celiac disease can be associated with occult gastrointestinal bleeding [92]. However, the positive results with colorimetric tests may have been due to excess loss of intestinal cells and/or malabsorption of peroxidase-containing foods rather than loss of red blood cells [93]. Furthermore, one study found that occult bleeding was no more common in patients with celiac disease compared with a control population [94]. Thus, occult gastrointestinal bleeding may not be a major contributor to iron deficiency.

**Metabolic bone disease** — Metabolic bone disease is common in celiac disease and can occur in patients without gastrointestinal symptoms [95-97]. In one study, for example, bone mineral density (BMD) and the prevalence of osteopenia and osteoporosis in 77 patients with celiac disease were compared with 157 controls [73]. Patients with celiac disease had significantly decreased BMD in the lumbar spine and femoral neck compared with controls (-6 and -5 percent, respectively). They were also significantly more likely to have osteoporosis of the lumbar spine (26 versus 5 percent). Osteoporosis of the femoral neck was uncommon in both groups. These patients have secondary hyperparathyroidism that is probably due to vitamin D deficiency [98]. Osteomalacia due to vitamin D deficiency is also sometimes seen, although its exact prevalence is unknown [99].

In adults, loss of bone density in the peripheral skeleton may persist despite apparent normalization at axial skeletal sites after patients are on a gluten free diet [98]. In contrast, in a study of 30 children and adolescents maintained on a long-term gluten-free diet (average 10.7 years), bone mineral density and serum markers of bone metabolism completely normalized [100]. These parameters

improved but did not reach normal levels in adults with late diagnosis and institution of a gluten-free diet [101]. In another report, a gluten-free diet for only one year significantly improved spinal and femoral neck bone density in 19 newly diagnosed adult patients with clinically silent celiac disease [97]. The American Gastroenterological Association (AGA) guideline for osteoporosis in gastrointestinal diseases [102], as well as other AGA guidelines, can be accessed through the AGA web site at <http://www.gastro.org/practice/medical-position-statements>.

The degree to which bone loss translates into an increased fracture risk in patients with celiac disease was investigated in a population-based cohort study that focused on 4732 patients with celiac disease who were compared with 23,620 age- and sex-matched controls [103]. The overall hazard ratio for any fracture was 1.3 (95 percent CI 1.16 to 1.46). The absolute difference in the overall fracture rate was 3.2 per 1000 person-years. These data suggest that the risk of fractures is only slightly increased in patients with celiac disease.

**Hyposplenism** — Several case reports have described hyposplenism in association with celiac disease [104-107], the pathogenesis of which is unknown. Prophylactic pneumococcal vaccination has been suggested. (See "[Approach to the adult patient with splenomegaly and other splenic disorders](#)", section on '[Hyposplenism and asplenia](#)'.)

**Kidney disease** — Glomerular IgA deposition is common, occurring in as many as one-third of patients. The great majority of affected patients have no clinical manifestations of renal disease, perhaps because there is no associated activation of complement. (See "[Pathogenesis of IgA nephropathy](#)".)

**Idiopathic pulmonary hemosiderosis** — Coexistence of celiac disease and idiopathic pulmonary hemosiderosis, also known as Lane-Hamilton syndrome, has been reported in a number of cases, and introduction of a gluten-free diet has been associated with remission of pulmonary symptoms in several patients. (See "[Idiopathic pulmonary hemosiderosis](#)".)

**RISK OF MALIGNANCY AND MORTALITY** — A number of observational studies have noted a small absolute increase in overall mortality in patients with celiac disease compared with the general population [108-117]. Estimates of the magnitude of risk have differed in various reports, many of which were small, based upon referral populations, and had several methodologic limitations. In addition, the increase in some studies was limited to non-Hodgkin's lymphoma [116,117].

The magnitude of mortality risk and its relation to small bowel histopathology was evaluated in a retrospective cohort study from Sweden that included approximately 29,000 individuals with celiac disease (diagnosed by villous atrophy on small bowel

biopsy), 13,000 individuals with only inflammation on biopsy, and 3700 individuals with normal mucosal histology but positive celiac disease serology (called latent celiac disease) [108]. At a median follow-up of seven to nine years, there was a significant absolute increase in mortality in all three groups (2.9, 10.8, and 1.7 per 1000 person years, respectively). The higher absolute mortality among patients with inflammation is partly explained by their older age at study entry. The increase in mortality was largely due to cardiovascular disease and malignancy.

A study of 9133 healthy adults who were in the United States Air Force evaluated stored sera collected between 1948 and 1954 [109]. A total of 14 patients (0.2 percent) were found to have undiagnosed celiac disease. Compared with an age-and sex-matched cohort who were seronegative, undiagnosed celiac disease was associated with an approximate fourfold increase in all-cause mortality.

Whether the degree of compliance with a gluten-free diet influences the rates of these cancers is uncertain. In one study, the increased risk of non-Hodgkin lymphoma persisted for five years after diagnosis despite adherence to a gluten-free diet [116].

- One of the largest population-based studies to address this issue included 12,000 patients with celiac disease or dermatitis herpetiformis identified from a Swedish registry between 1964 and 1994 [113]. Cancer was diagnosed in 249 patients during follow-up (standardized incidence ratio [SIR] 1.3, 95% CI 1.2 to 1.5), suggesting that the overall increase in cancer risk was modest, especially compared with previous reports. Furthermore, the risk declined with increasing length of follow-up and was not increased in children or adolescents. The most common malignancy was lymphoma (SIR 5.9), which accounted for 18 percent of all cancers (picture 3). The risk of lymphoma was considerably lower than in several earlier reports, in which the risk was estimated to be increased 15- to 100-fold. The risk of other digestive tract cancers was also increased, including oropharyngeal (mostly esophageal squamous cell), small intestinal adenocarcinoma, colorectal, and hepatocellular. In contrast, there was a significantly reduced risk of breast cancer. (See "[Clinical presentation and diagnosis of primary gastrointestinal lymphomas](#)".)
- Another population-based study from the United Kingdom compared 4732 people with celiac disease with 23,620 matched controls who were included in a database between 1987 and 2002 [118]. There were a total of 134 malignancies in the celiac group (2.8 percent). The overall risk of malignancy was increased by approximately 30 percent (hazard ratio [HR] 1.29, 95% CI 1.06-1.55). The risk was highest for lymphoproliferative disease (HR 4.80) and gastrointestinal cancer (HR 1.85). Most cancers were detected in the first

year after diagnosis. The study also confirmed a reduced risk of breast cancer (HR 0.35) and, in addition, found a reduced risk of lung cancer (0.34), the mechanisms for which are unclear.

**ASSOCIATED CONDITIONS** — Celiac disease is frequently associated with dermatitis herpetiformis, Down syndrome, selective IgA deficiency, and other conditions which have autoimmune features such as type 1 diabetes mellitus, thyroid disease, and liver disease. Patients with celiac disease (and their families) may also be more likely to have atopic dermatitis compared with the general population, although the prevalence of other allergies is not increased [[119](#)].

**Dermatitis herpetiformis** — Dermatitis herpetiformis is a condition characterized by pruritic papulovesicles over the external surface of the extremities and on the trunk ([picture 4](#)). The diagnosis is confirmed histologically by the demonstration of granular IgA deposits along the nonaffected subepidermal basement membrane. Similar to celiac disease, antibodies against tissue transglutaminase (anti-tTG) are elevated in patients with the disease. The autoantibodies are directed mainly against epidermal transglutaminase, which shows high sequence homology to tTG [[120](#)]. Compared with endomysial antibodies, anti-tTG antibodies had a sensitivity of 98 percent and specificity of 89 percent in a study involving 61 patients with dermatitis herpetiformis who were compared with 84 controls [[121](#)].

Dermatitis herpetiformis is common among patients with celiac disease. In an illustrative study, celiac disease was diagnosed in 398 of 147,000 people (prevalence of 1:369) in a population-based study in Finland, of whom 24 percent had dermatitis herpetiformis [[122](#)]. However, the prevalence of dermatitis among celiac patients may have been overestimated since the prevalence of celiac disease was lower than has been described in other reports [[22](#)]. Precise estimates of the converse (ie, the proportion of patients with dermatitis herpetiformis who have celiac disease) are uncertain, but are probably in the range of 85 percent when the diagnosis of celiac disease has been based upon a mucosal biopsy [[123](#)].

Dermatitis herpetiformis and celiac disease are associated with the same HLA-DQ alpha beta heterodimers, and dermatitis herpetiformis shares an association with other autoimmune conditions [[124-126](#)]. Although the celiac disease in patients with dermatitis herpetiformis is often asymptomatic, the skin lesions in most patients respond to gluten withdrawal [[127](#)].

**Diabetes mellitus** — Celiac disease is closely associated with type 1 diabetes mellitus [[128-131](#)]. In several reports, between 2.6 and 7.8 percent of adults with type 1 diabetes had IgA autoantibodies to endomysium or to tissue transglutaminase; most such patients were proven to have celiac disease with small bowel biopsy [[132,133](#)]. Many such patients had no overt clinical manifestations of celiac disease [[132](#)]. Other reports have demonstrated that as

many as 3.5 percent of children of parents with type 1 diabetes have celiac disease, the prevalence of which increases with age [134].

Type 1 diabetes and celiac disease share multiple genetic loci such as HLA-DR3, HLA-DQ2 (HLA-DQ8) and several genetic variations [13,111,135]. This suggests that type 1 diabetes and celiac disease have common features in their pathogenesis such as tissue damage from autoimmunity or intolerance to dietary antigens. Approximately one-third of type 1 diabetics who have the celiac disease-predisposing haplotype HLA-DQ2 (which is found in 20 to 25 percent of the general Western population) have raised IgA autoantibodies to tissue transglutaminase and are therefore likely to have celiac disease [136]. This is in comparison to a prevalence of tissue transglutaminase autoantibodies in only 2 percent of those without HLA-DQ2.

The age of onset and the severity of diabetes do not appear to be influenced by the presence of celiac disease [132]. Furthermore, celiac disease does not appear to trigger autoimmunity leading to diabetes as suggested in one report [137] since celiac autoantibodies usually develop after the onset of diabetes [138].

Whether a gluten-free diet improves diabetes in diabetic patients with celiac disease is unclear. Only two small studies, one retrospective [139] and one short-term [129], investigated the effect of a strict gluten-free diet on type 1 diabetics with silent celiac disease. Patients showed at best a trend toward an increased body mass index, but no change in folate or hemoglobin levels or insulin requirements. However, animal studies suggest that the interplay between gluten exposure and the intestinal immune system can modulate the development of type 1 diabetes. Substitutions of hydrolyzed casein instead of gluten in the diet delayed the onset of type 1 diabetes in BB rats, which spontaneously develop diabetes [140], and a gluten-free diet reduced the incidence of type 1 diabetes in non-obese diabetic (NOD) mice from 64 to 15 percent [141]. Furthermore, the very early supplementation of newborns diet with gluten (<3 months) showed an increased risk for islet autoantibodies, which precede type 1 diabetes mellitus [142]. Thus, larger and prospective clinical studies are required to clarify the relationship between celiac disease, type 1 diabetes, and other secondary autoimmunities.

**Selective IgA deficiency** — An association between selective IgA deficiency and celiac disease appears to be well-established as screening programs have detected celiac disease in up to 8 percent of patients [143]. On the other hand, selective IgA deficiency occurs in 1 to 2 percent of patients with celiac disease [144]. Screening for celiac disease in patients with IgA deficiency is best done using an IgG test for tissue transglutaminase. (See "[Diagnosis of celiac disease](#)".)

**Down syndrome** — There appears to be a strong association between Down syndrome and celiac disease. The prevalence of biopsy proven celiac disease has



been reported to be as high as 16 percent, representing a 20-fold increase compared with the general population [[145,146](#)].

**Liver disease** — As mentioned above, celiac disease may be associated with nonspecific mild chronic elevation in serum aminotransferase levels (AST ranging from 29 to 80, and ALT ranging from 60 to 130 with the ALT usually slightly greater than AST [[147,148](#)]). Celiac disease accounted for 4 percent of abnormal liver function tests of unexplained etiology in a series of 2,512 patients [[149](#)]. The disease was histologically confirmed by duodenal biopsy only in patients who tested positive for both anti IgG and IgA tissue-transglutaminase.

Celiac disease has also been associated with advanced liver disease [[150-152](#)]. One report, for example, focused on four patients with severe liver disease (due to congenital liver fibrosis, massive steatosis, and progressive hepatitis of unclear origin) and untreated celiac disease. Hepatic dysfunction reversed in all patients following a gluten-free diet [[153](#)]. Celiac disease was also identified in 8 of 185 adult patients who had undergone liver transplantation. In six, celiac disease had been identified preoperatively; liver disease was due to primary biliary cirrhosis, autoimmune hepatitis, primary sclerosing cholangitis, or congenital liver fibrosis. Two additional patients with celiac disease were identified through screening (one with autoimmune hepatitis and one with primary sclerosing cholangitis). Although the number of patients studied is small, these data suggest that celiac disease may contribute to or be the cause of serious liver disease, which may improve following a gluten-free diet.

The association between celiac disease and primary biliary cirrhosis (PBC) has also been described in other reports [[151](#)]. Two studies suggested a prevalence of 6 to 11 percent in patients with PBC [[154,155](#)], although these may be overestimates. No cases of celiac disease were detected in 65 patients with PBC in a study from Italy [[156](#)]. Recognition of celiac disease in patients with PBC may be important since both diseases impact negatively upon bone mineralization and are risk factors for osteoporosis. (See "[Metabolic bone disease in primary biliary cirrhosis](#)".)

One study evaluated the risk of liver disease in 13,818 patients with celiac disease from 1964 to 2003, with 66,584 age- and sex-matched controls [[152](#)]. Celiac disease was associated with an increased risk of acute hepatitis, chronic hepatitis and primary sclerosing cholangitis. Adjustment for socioeconomic index or diabetes mellitus had no notable effect on the risk estimates. In addition, prior liver disease was associated with a statistically significant four- to six-fold increased risk of later celiac disease.

**Thyroid disease** — There is an increased incidence of autoimmune thyroid disease among patients with celiac disease [[157,158](#)]. Hypothyroidism is more frequent than hyperthyroidism.

**Menstrual and reproductive issues** — Women with untreated celiac disease may have an increased frequency of reproductive abnormalities: later menarche, earlier menopause, secondary amenorrhea, recurrent miscarriage, and infertility [159-163]. However, on a population basis, women with celiac disease have similar overall fertility to the general female population [164]. In addition, a cohort study, which included 211 newborns, found a threefold higher risk of intrauterine growth restriction among infants of mothers with undiagnosed celiac disease compared with controls [165]. Treatment of celiac disease appears to prevent these problems.

Male infertility, characterized by abnormalities in sperm motility and morphology as well as a biochemical picture of androgen resistance (high serum testosterone and high LH concentrations), has been reported in celiac disease [166,167]. In one study of 41 men with celiac disease and high testosterone and LH concentrations, dietary modification led to normalization of the biochemical abnormalities [167]. (See "[Causes of male infertility](#)".)

**Myocarditis and cardiomyopathy** — Two reports from Italy suggest that celiac disease, which is often clinically unsuspected, accounts for as many as 5 percent of patients with autoimmune myocarditis or idiopathic dilated cardiomyopathy [168,169]. In one report of nine such patients, none had classic gastrointestinal symptoms of celiac disease (recurrent abdominal pain, diarrhea, and weight loss), but all had iron deficiency anemia refractory to oral iron replacement [168]. Cardiac function improved following a gluten-free diet with or without immunosuppressive therapy. (See "[Etiology and pathogenesis of myocarditis](#)", section on 'Celiac disease'.)

**Atrophic glossitis** — Oral lesions (erythema or atrophy) and a soreness or burning sensation of the tongue have been described in association with celiac disease and respond to a gluten free diet [170]. Oral symptoms are frequent in patients with classical celiac disease, thus the involvement of the oral cavity is a helpful tool in diagnosis of celiac disease [171].

**Pancreatitis** — A large database study described an increased risk of pancreatitis (both acute and chronic) in patients with celiac disease diagnosed in adulthood [172]. Further studies are needed to clarify the strength of the association and potential mechanisms that underlie it.

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "[Patient information: Celiac disease in adults](#)".) We



encourage you to print or e-mail this topic review, or to refer patients to our public web site, [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

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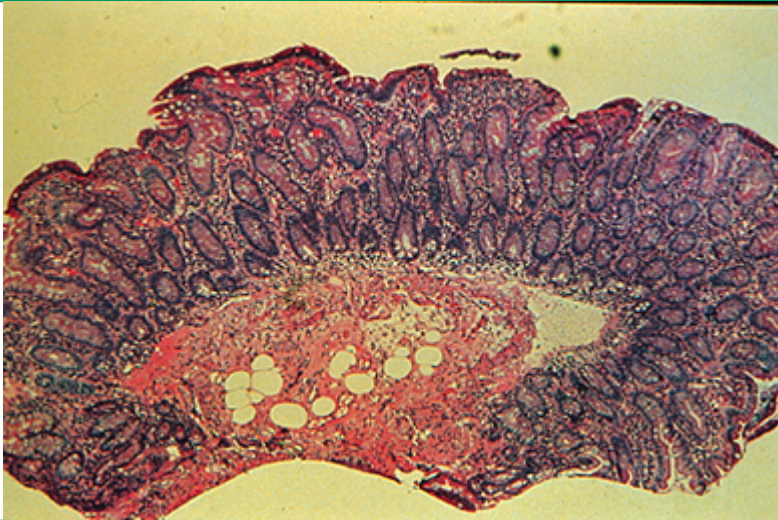
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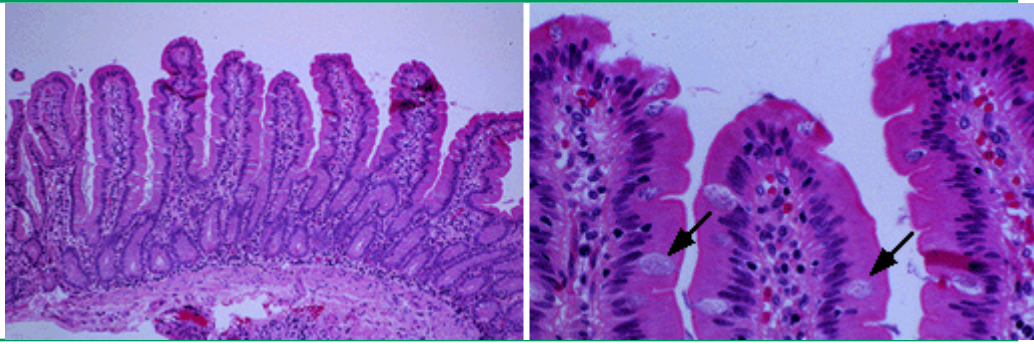
## GRAPHICS

### Celiac disease



Low power view of a small bowel biopsy from a patient with celiac disease. The mucosa is flat with complete loss of the normal villous architecture. *Courtesy of Robert Odze, MD.*

## Normal small intestine



Low (left) and high (right) power views of the normal villous architecture of the small intestine. The high power view shows the enterocytes and interspersed goblet cells (arrows). *Courtesy of Robert Odze, MD.*

**Positive predictive value of serum tests for celiac disease based upon 4615 adults in Northern Italy**

<b>Serum test</b>	<b>Probability*, percent</b>
IgA antiendomysium	100
IgG antigliadin	2
IgA antigliadin	12
IgG and IgA antigliadin	33

\* Indicates probability that the disease is present when the test is positive. *Adapted from: Pittschieler, K, Ladinser, B, Acta Paediatr 1996; 412(Suppl):42.*

## Prevalence of celiac disease in 17,201 Italian school children (age 6 to 15)

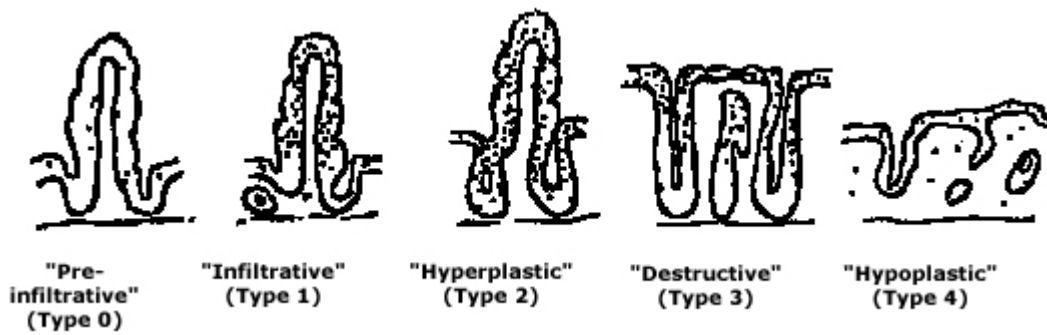
Test	Percent positive
IgG and/or IgA antigliadin antibodies	7.50
IgA antigliadin and/or IgA endomysial antibodies	0.65
Intestinal biopsy performed	0.57
Villous atrophy seen on biopsy	0.44
Not biopsied but clinically celiac	0.04
Previously known celiac	0.06
<b>TOTAL with diagnosis of celiac disease</b>	<b>0.54</b>

*Adapted from: Catassi, C, Fabiani, E, Ratsch, IM, et al, Acta Pediatr 1996; 412(Suppl):29.*



## Intestinal lesions in celiac disease

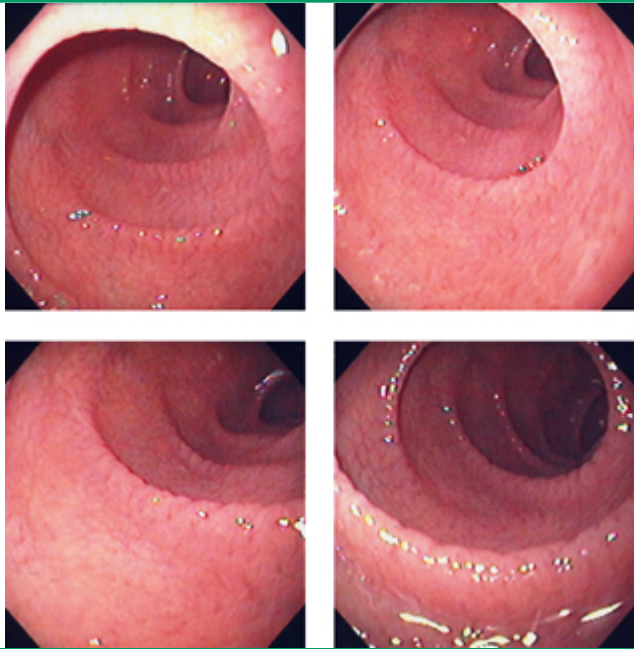
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Schematic representation of the five main lesions associated with gluten sensitivity. The lesions range in histologic severity from a mild alteration characterized by increased intraepithelial lymphocytes (type 0 lesion) to a flat mucosa with total mucosal atrophy, complete loss of villi, enhanced epithelial apoptosis and crypt hyperplasia (type 3 lesion). The type 4 lesion is seen in T cell lymphoma. *Adapted from Marsh, MN, Gastroenterology 1992; 102:330.*

## Celiac disease

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Scalloped duodenal folds seen on endoscopy in a patient with celiac disease. *Courtesy of Eric D Libby, MD.*

## Clinical and laboratory findings in 82 oligosymptomatic Italian children with celiac disease detected by screening

Symptom	Percent
Iron deficiency	
With anemia	29
Without anemia	27
Recurrent abdominal pain	24
Mood changes	17
Recurrent aphthous stomatitis	11
Poor appetite	10
Recurrent diarrhea	9
Short stature	7
Abdominal distention	5
Constipation	2
Pubertal delay	2
Hypoalbuminemia	2

Data from: Catassi, C, Fabiani, E, Räscher, IM, et al, *Acta Paediatr* 1996; 412(Suppl):29.

## Nongastrointestinal nonmalignant symptoms of celiac disease

Infertility
Rheumatic disorders
Vitamin D and calcium deficiency
Osteomalacia
Osteoporosis
Neurologic disorders
Depression - 10.6 percent
Epilepsy - 3.5 percent
Migraine headaches - 3.2 percent
Anxiety - 2.6 percent
Suicidal tendency - 2.1 percent
Carpal tunnel syndrome - 1.8 percent
Myopathy - 1.5 percent

*Data from: Holmes, JKT, Acta Paediatr 1996; 412(Suppl):68.*

## Lymphoma arising in celiac disease

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Small bowel follow through examination shows a large ulcerating extrinsic mass (white arrow) arising between and displacing loops of jejunum in a patient with celiac disease. Note the distended, featureless loops of jejunum, which have lost their normal fold pattern; these features are characteristic of celiac disease. *Courtesy of Jonathan Kruskal, MD, PhD.*

## Dermatitis herpetiformis



Herpetiform clusters of vesicles on an erythematous, edematous base with crusts and postinflammatory pigmentation on the upper back and shoulder. *Reproduced with permission from: Skin signs of immune, autoimmune, and rheumatic diseases. In: Color Atlas and Synopsis of Clinical Dermatology, 3rd ed, Fitzpatrick, TB, Johnson, RA, Wolff, K (Eds), McGraw-Hill, New York 1997. p.327. Copyright © 1997 McGraw Hill.*





## Diagnosis of celiac disease

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**INTRODUCTION** — Celiac disease can be defined as a small bowel disorder characterized by mucosal inflammation, villous atrophy, and crypt hyperplasia, which occur upon exposure to dietary gluten and which demonstrate improvement after withdrawal of gluten from the diet. However, the availability of serologic testing for celiac disease and the common use of upper endoscopy has complicated the definition, since these tests have identified patients who appear to have the disease but have variable degrees of histopathologic changes and/or symptoms. Thus, several categories of celiac disease have emerged. Whether these phenotypes are clinically useful remains to be determined [1,2]:

- The classical form, characterized by fully developed villous atrophy and features of intestinal malabsorption.
- The atypical form, characterized by fully developed villous atrophy in the setting of milder clinical features such as iron deficiency, osteoporosis, short stature, and/or infertility. Despite the historical title of "atypical", this form is the most common.
- The silent form in which villous atrophy is found after testing asymptomatic patients (eg, because of a family history of celiac disease or during an upper endoscopy performed for another reason).
- A potential form in those who have never had a biopsy consistent with celiac disease, but show serologic and/or immunologic abnormalities characteristic for the disorder. This is most often detected in patients with a family history of celiac disease.
- A latent form in patients who had a previous diagnosis of celiac disease that responded to gluten withdrawal but retained normal villous architecture after



gluten reintroduction. The latent form also refers to patients with elevated IgA tTG serology but normal intestinal mucosa who may subsequently develop celiac disease.

The natural history of these various forms of celiac disease is incompletely understood. In particular, the long-term risk of complications in patients who are asymptomatic is unclear. Such patients may also be least likely to comply with a gluten free diet. (See ["Management of celiac disease in adults"](#).)

This topic review will focus on the use of serum antibodies in the diagnosis and management of celiac disease. This topic is also discussed in an official position statement issued by the American Gastroenterological Association [3]. Guidelines have also been issued by other organizations, including a 2004 consensus statement from the National Institutes of Health (NIH) [2]. The subsequent discussions are consistent with the NIH guidelines. General recommendations for diagnosis are presented at the end (see ["Summary and recommendations"](#) below).

**WHO SHOULD BE TESTED** — Testing for celiac disease should be considered in the following groups of patients [2]:

- Those with gastrointestinal symptoms including chronic or recurrent diarrhea, malabsorption, weight loss, and abdominal distension or bloating. This includes patients with symptoms suggestive for irritable bowel syndrome or severe lactose intolerance.
- Individuals without other explanations for signs and symptoms such as iron deficiency anemia, folate or vitamin B12 deficiency, persistent elevation in serum aminotransferases, short stature, delayed puberty, recurrent fetal loss, low birthweight infants, and reduced fertility persistent aphthous stomatitis, dental enamel hypoplasia, idiopathic peripheral neuropathy, nonhereditary cerebellar ataxia, or recurrent migraine headaches.
- Symptomatic individuals at high risk for celiac disease including patients with type 1 diabetes mellitus or other autoimmune disorders, first- and second-degree relatives of individuals with celiac disease, patients with Turner, Down, or Williams syndromes.

As will be discussed below, screening of the general population is not recommended. Screening of patients with osteoporosis is also not recommended in the consensus statement since the prevalence of celiac disease is not significantly increased among the general population of patients with osteoporosis.

However, this conclusion was not supported by a study published after the consensus conference in which the prevalence of celiac disease in 260 men and

women with osteoporosis was compared with 575 controls without osteoporosis [4]. The prevalence of biopsy proven celiac disease was significantly higher in the osteoporosis group (3.4 versus 0.2 percent). Most patients had biochemically evident secondary hyperparathyroidism with vitamin D deficiency. Furthermore, all but one had other clinical features suggestive of celiac disease including anemia, weight loss, or gastrointestinal symptoms. Thus, until further data are available, screening patients with osteoporosis for celiac disease should probably be confined to those with additional clinical or laboratory features suggestive of the disorder and those with known risk factors for celiac disease.

**DIAGNOSTIC APPROACH** — An approach to diagnosis of celiac disease is summarized in the following algorithm ([algorithm 1](#)). All testing should be performed while patients are on a gluten-rich diet. No single test can confidently establish the diagnosis of celiac disease in every individual. As a result, the most important initial step in diagnosis is recognition of the many clinical features that can be associated with the disease.

**Serologic evaluation** — As a general rule, testing should begin with serologic evaluation. As will be discussed below, the most sensitive and specific tests are IgA anti tissue transglutaminase and IgA endomysial antibody, which have equivalent diagnostic accuracy.

By contrast, antigliadin antibody tests are no longer used routinely because of their lower sensitivity and specificity. However, a second generation AGA test (Deamidated Gliadin Peptide (DGP)) yielded far higher diagnostic accuracy (sensitivity 94 percent, specificity 99 percent) [5,6]. The DGP uses synthetic gliadin peptides that mimic tTG-modified gliadin sequences to capture serum IgA or IgG against DGP. If these initial data are reproducible in practice, the combination of anti-tTG and DGP serology may become a powerful non-invasive pairing for serologic diagnosis of celiac disease. Serologic testing may not be as accurate in children less than age five and is less accurate before age two.

**Testing on a gluten-rich diet** — All diagnostic tests should be performed while the patient is on a gluten-rich diet. Some patients may have already begun a low gluten diet before undergoing formal evaluation and thus may have normal results from antibody testing. Such patients should be advised to consider resuming a gluten-rich diet for 2 to 12 weeks before antibody titers are drawn. This recommendation was based upon studies in children, which have suggested that approximately 75 percent of patients will have abnormal antibody levels within two to four weeks [7,8].

At least one study in adults found that three weeks of ingestion of a gluten-containing diet in patients with histologically proven celiac disease in remission was insufficient to achieve an increase in antibody titers, although the patients

experienced worsening of symptoms and developed carbohydrate and fat malabsorption [9]. The authors suggested that tests of malabsorption rather than antibody tests are preferred when attempting to diagnose celiac disease in patients already consuming a gluten-free diet. However, the traditional approach of performing a small bowel biopsy after a period of "gluten challenge" remains the gold standard for diagnosis.

Antibody levels remain elevated for varying lengths of time (1 to 12 months) after patients with celiac disease begin a gluten free diet. Thus, antibody testing in patients who have only recently begun a gluten free diet is reasonable and may yield a positive result, although testing while on a gluten containing diet is preferable to exclude celiac disease.

**Small bowel biopsy** — Patients with a positive IgA endomysial or transglutaminase antibody test should undergo a small bowel biopsy. Exceptions are those who have biopsy-proven dermatitis herpetiformis in whom the diagnosis can be established without a small bowel biopsy.

Multiple biopsies should be obtained in the second and third portion of the duodenum. The exact minimal number is uncertain, although some experts believe that at least four should be obtained [10,11]. The duodenal mucosa may appear atrophic with loss of folds, contain visible fissures, have a nodular appearance or the folds may be scalloped (picture 1), but such findings are not universally present and may be seen with other disorders (table 1) [12]. Staining techniques and high resolution magnification endoscopy can help identify areas of villous atrophy for biopsy [13-15].

The diagnosis is presumptively established when there is concordance between the serologic results and the biopsy findings. It is confirmed when symptoms resolve subsequently on a gluten-free diet. Demonstration of histologic normalization is not always required.

**Suggestive clinical features but negative serologic tests** — There are three main possibilities in those with suggestive clinical features but negative serologic tests:

- The individual may have selective IgA deficiency. In such patients, testing for IgG anti tissue transglutaminase antibodies, IgG endomysial antibodies and/or IgG deamidated gliadin peptide antibodies should be performed.
- The individual may already be on a low gluten diet.
- The serologic test could be falsely negative in which case a small bowel biopsy is needed to make a diagnosis.

- The patient may not have celiac disease in which case other causes of symptoms or villous atrophy should be considered ([table 1](#)).

There are occasional patients in whom the diagnosis is unclear despite the above. Such patients can undergo testing for HLA haplotypes associated with celiac disease. More than 99 percent of patients with celiac disease have HLA DQ2 and/or DQ8 compared with about 40 percent of the general population. Thus, celiac disease is highly unlikely in patients without these haplotypes [[16](#)].

**Positive serologic tests but negative small bowel biopsies** — IgA tTG serology may occasionally be positive but the small intestinal biopsy normal. False positive tTG results are rare but do occur and are usually low titer (typically less than twice the upper limit of normal). Repeating the test using an assay that uses human tTG as the capture antigen may resolve the discrepancy since older tTG tests using non-human tTG have more frequently been associated with false positive results. The intestinal biopsy should be reviewed by a pathologist familiar with CD to look for subtle abnormalities of CD such as an increase in IELs. If these two steps do not reconcile the results, the patient can be placed on a high gluten diet and, after 6 to 12 weeks, numerous additional biopsies obtained from multiple sites in the mid and distal duodenum since CD enteropathy can be patchy and missed due to sampling error. As noted above, staining techniques and high resolution magnification endoscopy can help identify areas of villous atrophy for biopsy.

Some patients have a positive serologic test and only mild histologic changes supportive of celiac disease. Patients with mild villous atrophy appear to benefit from a gluten free diet. The response to gluten free diet in patients with an increase in intraepithelial lymphocytes but normal villi is less clear [[17](#)].

There may be a subset of patients with clinical features resembling IBS who do not have a serologic or histologic profile diagnostic of celiac disease but who may respond symptomatically to a gluten free diet. One study suggested that the presence of serum IgG antigliadin antibodies and expression of HLA-DQ2 may be predictive of such a response in patients with diarrhea-predominant IBS but the strength of the association remains unclear [[18](#)].

**SERUM ANTIBODY ASSAYS** — A variety of serologic studies have been described to aid in the diagnosis of celiac disease, including:

- IgA endomysial antibody (IgA EMA)
- IgA tissue transglutaminase antibody (IgA tTG)
- IgA antigliadin antibody (IgA AGA)
- IgG antigliadin antibody (IgG AGA)

Serum IgA endomysial and tissue transglutaminase antibody testing have the highest diagnostic accuracy. The IgA and IgG antigliadin antibody tests have lower diagnostic accuracy with frequent false positive results and are therefore no longer recommended for initial diagnostic evaluation or screening [2]. However, the newer anti-deamidated gliadin peptide assays described above may result in the re-introduction of AGA testing in celiac disease. IgA EMA, IgA tTG, and IgA AGA levels fall with treatment; as a result, these assays can be used as a noninvasive means of monitoring the response to a gluten-free diet. (See '[Monitoring adherence and response to gluten free diet](#)' below.)

Serologic studies for celiac disease can be divided into two groups based upon their target antigens: antiendomysial and antigliadin antibody tests [19].

**IgA endomysial assay** — Endomysial antibodies bind to connective tissue surrounding smooth muscle cells [19-26]. Frozen sections of monkey esophagus were initially used for the assay. Currently, many laboratories use sections of human umbilical cord which are more readily available [27,28]. Serum IgA endomysial antibodies bind to the endomysium, producing a characteristic staining pattern, which is visualized by indirect immunofluorescence [29,30]. The test result is reported simply as positive or negative since even low titers of serum IgA endomysial antibodies are specific for celiac disease. The target antigen has been identified as a tissue transglutaminase (see below).

IgA endomysial antibody testing is moderately sensitive and highly specific for untreated celiac disease [19-23,25,26]. Serum levels of IgA endomysial antibody fall on a gluten-free diet and the test often becomes negative in treated patients [24].

**Anti-tissue transglutaminase antibodies** — The antigen against which antiendomysial antibodies are directed is a tissue transglutaminase (tTG) [31]. Anti-tTG antibodies were highly sensitive and specific for the diagnosis of celiac disease in most reports [32-36]. In an illustrative series, anti-tTG antibodies were present in 98 percent of patients with biopsy-proven celiac disease compared to 5 percent of controls [32]. In another study that included 136 patients with celiac disease and 207 controls, the sensitivity and specificity of anti-tTG antibodies was 95 and 94 percent, respectively [33].

ELISA tests for IgA anti-tTG antibodies are now widely available and are easier to perform and less costly than the immunofluorescence assay used to detect IgA endomysial antibodies. The diagnostic accuracy of IgA anti-tTG immunoassays has been improved further by the use of human tTG in place of the non-human tTG preparations used in earlier immunoassay kits [37].

**Antigliadin antibody assays** — Gliadin is a component of the wheat storage

protein gluten. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".) Purified gliadin is readily available and is used as the antigen for enzyme-linked immunosorbent assays (ELISA) to detect serum antigliadin antibodies.

Serum antigliadin antibody levels are frequently elevated in untreated celiac disease, and antigliadin assays have been used for some years as a diagnostic aid [[19,20,22,38-47](#)]. Although these tests demonstrate moderate sensitivity and specificity, with the IgA tests being marginally superior, their positive predictive value in a general population is relatively poor ([table 2](#)). In one series, as an example, the positive predictive value for IgG antigliadin antibodies corrected for the expected prevalence in the general population was <2 percent [[48](#)].

Antigliadin antibody test results are reported as a titer or level. A high titer of antigliadin antibody is somewhat more specific for celiac disease than a low titer, but some normal individuals have high serum levels of antigliadin antibody. Antigliadin antibody levels decrease during treatment with a gluten-free diet.

**Assay sensitivity and specificity** — A systematic review of the literature estimated that the sensitivity and specificity of IgA endomysial and IgA tissue transglutaminase antibodies were over 95 percent and close to 100 percent, respectively [[1](#)]. However, the literature reports wide variations in test sensitivity and specificity among different laboratories [[19,49](#)].

It is therefore important to know the sensitivity and specificity of the assay as performed by the testing laboratory before determining the clinical significance of a particular test result. The following data come from our experience [[40,41](#)]:

- IgA endomysial antibodies — sensitivity 85 to 98 percent; specificity 97 to 100 percent
- IgA tissue transglutaminase antibodies — sensitivity 90 to 98 percent; specificity 95 to 97 percent
- IgA antigliadin antibodies — sensitivity 80 to 90 percent; specificity 85 to 95 percent
- IgG antigliadin antibodies — sensitivity 75 to 85 percent; specificity 75 to 90 percent

It is also important to consider the likelihood that the patient has the disease since, at a given sensitivity and specificity, the pretest probability of disease determines the positive and negative predictive values of the test (see '[Clinical application of serologic tests](#)' below).

In addition to laboratory variation, the sensitivity of these tests may depend upon the severity of the disease. In one report, as an example, serum antibodies were determined in 101 patients with biopsy proven celiac disease [[50](#)]. The sensitivity

of IgA endomysial antibodies varied from 100 percent in patients with total villous atrophy to only 31 percent in those with partial villous atrophy.

**Role of antibodies in disease pathogenesis** — Antigliadin antibodies do not appear to be essential for the pathogenesis of celiac disease [19]. Furthermore, many normal individuals have increased IgA and/or IgG antigliadin levels [39,51]. In contrast, IgA endomysial antibodies are rarely found in the absence of gluten-sensitive enteropathy. However, patients with celiac disease who lack these antibodies do not differ in their clinical presentation from those who are antibody positive. Nevertheless, there is some evidence to suggest that, in addition to cellular immunity, antibodies against tissue transglutaminase, the target autoantigen within the endomysium, are of some pathogenetic importance. Furthermore, tissue transglutaminase enzymatically alters gliadin peptides to increase their propensity to induce helper T-cell activation when presented by DQ2 or DQ8 on antigen presenting cells. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".)

Individuals with celiac disease also have increased levels of serum antibodies against other food proteins such as beta-lactoglobulin, casein, and ovalbumin [52]. It is not clear whether this reflects a general aberrant immune responsiveness to food antigens or results from enhanced systemic exposure to these proteins because of increased small intestinal permeability.

**CLINICAL APPLICATION OF SEROLOGIC TESTS** — Three different clinical circumstances should be considered when using serologic studies in the diagnosis and management of celiac disease:

- Evaluation of individuals with a low pretest probability for celiac disease. Such patients may have undergone testing for celiac disease during evaluation of common disorders such as irritable bowel syndrome, reduced fertility or osteoporosis.
- Evaluation of individuals with a moderate or high pretest probability for celiac disease
- Monitoring adherence and response to a gluten-free diet

**Individuals with a low risk for celiac disease** — When the pretest probability of celiac disease is perceived to be low (ie, less than 5 percent), serologic studies are useful in excluding the diagnosis. Asymptomatic patients without a family history of celiac disease or laboratory or clinical evidence for malabsorption can be considered to be low risk. The patient's ethnicity may also help determine baseline risk. While celiac disease affects persons of many ethnic backgrounds, it is rare in those of purely Chinese, Japanese, or Sub-Saharan African descent.



In the low-risk setting, the IgA endomysial antibody test has the highest diagnostic accuracy but is a little more costly than the IgA tTG ELISA test ([algorithm 1](#)) [[19,22](#)]. The antigliadin antibody tests have lower diagnostic accuracy.

As noted above, the serum IgA antigliadin and IgA endomysial tests have similar sensitivities. A negative result for either test has a high negative predictive value in this situation and may obviate the need for small bowel biopsy.

The IgG antigliadin test is less sensitive and therefore less useful. IgG antigliadin is usually positive in the 1 to 2 percent of celiac patients who have IgA deficiency [[53,54](#)]. Many clinicians test simultaneously for both IgA and IgG antigliadin [[19,20](#)]. This approach gives a small incremental increase in sensitivity but increases cost and leads to frequent false positive test results, especially with the IgG antigliadin test. As a result most experts advise against routine AGA testing. The newer DGP tests are more specific and may be used to supplement tTG testing. IgA tTG titers will be very low in patients with celiac disease and IgA deficiency [[55](#)]. IgG DGP testing can be used in patients with IgA deficiency.

The specificities of the IgA endomysial and IgA tissue transglutaminase tests are high. Thus, their positive predictive values are high even in low-risk populations [[22,23,26](#)]. In contrast, the specificities of IgA and IgG antigliadin tests are lower, and positive results have a low positive predictive value in low-risk populations [[23,51,56](#)]. (See '[Screening in asymptomatic individuals](#)' below.)

In summary, a positive IgA tissue transglutaminase or endomysial antibody test is highly specific ([algorithm 1](#)). The standard antigliadin antibody tests have lower diagnostic accuracy and are no longer recommended because they yield many false positive results (15 to 20 percent of subjects tested) leading to unnecessary endoscopy with biopsy.

**Individuals with a moderate or high risk for celiac disease** — When the pretest probability of celiac disease is perceived to be high (ie, greater than 5 percent), diagnosis is based upon serologic tests and histology. Celiac disease is frequently associated with dermatitis herpetiformis, Down syndrome, selective IgA deficiency, and other conditions that have autoimmune features such as type 1 diabetes mellitus, thyroid disease, and autoimmune liver disease. Patients with these conditions or a family history of celiac disease can be considered as being at increased risk. Patients with suggestive clinical features such as severe diarrhea, weight loss, or persistent anemia can also be considered to be at high risk.

The standard approach has been to obtain a small bowel biopsy for histopathologic examination. However, the very high specificity of the IgA endomysial test has led to debate as to whether a positive result in the appropriate clinical setting can be considered diagnostic and eliminate the need for small bowel biopsy. We

recommend performing both IgA endomysial (or TTG) and small bowel biopsy prior to dietary treatment ([algorithm 1](#)). This approach provides the best means of making a definitive diagnosis of celiac disease from the outset.

Antigliadin antibody tests are not helpful when there is a moderate or high probability of celiac disease. A positive or negative result will not alter the need for small bowel biopsy and definitive histologic diagnosis. Since antigliadin antibody tests have a high false positive rate there is no role for a trial of a gluten-free diet for presumed celiac disease based on the finding of an elevated antigliadin antibody level.

**Monitoring adherence and response to gluten free diet** — The IgA antigliadin antibody assay was previously the most frequently used test for this indication [[20,41,43](#)]. However, with increased use of IgA tTG for initial diagnosis this assay is now also increasingly used in monitoring response to gluten free diet.

For whichever assay that will be used, a pretreatment antibody level should be determined at the time of diagnosis. Exclusion of gluten from the diet results in a gradual decline in serum IgA antigliadin and IgA tTG levels (half-life of six to eight weeks). A normal baseline value is typically reached within three to twelve months depending upon the pre-treatment concentrations. Normal IgA tTG levels do not reliably indicate recovery from villous atrophy [[36](#)]. Conversely, if the levels do not fall as anticipated, the patient is usually continuing to ingest gluten either intentionally or inadvertently ([figure 1](#)) [[40](#)].

Although the general patterns above can be helpful, the accuracy of these tests in establishing compliance with a gluten free diet is unsettled [[36,57](#)]. The value of these tests in monitoring adherence to a gluten-free diet is particularly limited in three respects:

- The test is useless if antibody levels are not elevated prior to therapy.
- Interassay variations in test results may be substantial and make interpretation difficult. Ideally, sera should be stored and assayed in parallel to avoid variations caused by interassay artifact. However, this approach is seldom practical. Serial samples should certainly be sent to one laboratory for testing to keep interassay variation to a minimum. Minor fluctuations in IgA antigliadin or IgA TTG levels are the norm and their importance should not be overinterpreted.
- Persistently high antibody levels usually reflect continued exposure to substantial amounts of dietary gluten. However, antibody levels will fall when dietary gluten intake is reduced, and they are not a sensitive indicator of occasional or minor dietary transgressions [[58](#)].

Serum IgG antigliadin and IgA endomysial antibody levels also fall when patients with celiac disease adhere to a strict gluten-free diet [[20,24,25](#)]. However, the decline in IgG antigliadin is more gradual than for IgA antigliadin [[41,43](#)], making it less useful in monitoring recent dietary adherence. IgA endomysial antibody levels are more costly and results are more difficult to quantify than IgA antigliadin or IgA tTG.

Other methods for assessing compliance continue to be developed. One group proposed a short survey that on initial evaluation was a more accurate predictor of compliance with a gluten free diet than serologic testing compared with a formal nutritional assessment as the reference standard [[59](#)]. Additional validation studies are needed.

**SCREENING IN ASYMPTOMATIC INDIVIDUALS** — Screening studies suggest that the incidence of celiac disease in whites of northern European ancestry may be as high as 1:100 to 1:250. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".)

The benefit of population screening for asymptomatic celiac disease, usually using the IgA endomysial or IgG tTG (transglutaminase) assays [[23,26,39,51,60](#)], has not yet been demonstrated. The potential advantages of screening for asymptomatic celiac disease include a reduction in risk for enteropathy-associated T-cell lymphoma, a reversal of unrecognized nutritional deficiency states, resolution of mild or ignored intestinal symptoms, avoidance of other autoimmune disorders, an improvement in general well-being, and a possible reduction in mortality. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".)

These issues were addressed in a 2009 report from the Mayo Clinic in which serum was tested for endomysial antibodies and, if positive, for tTG in almost 22,000 individuals from different time periods [[60](#)]. The following findings were noted:

- Among 9133 healthy young adults at an Air Force base in Minnesota in whom blood was obtained between 1948 and 1954, 14 (0.2 percent) had undiagnosed celiac disease. At a follow-up of 45 years, these individuals had a significant increase in mortality compared to those who were seronegative (hazard ratio 3.9).
- The rate of seropositivity was fourfold higher in samples obtained in a recent Olmsted County cohort matched for age or year of sampling. The rate of undiagnosed celiac disease was 4.0 to 4.5 times higher than in the original cohort (0.8 to 0.9 versus 0.2 percent), suggesting a dramatic increase in prevalence.

The possible benefits of screening and subsequent therapy depend upon compliance with an exacting, sometimes expensive, dietary regimen. Asymptomatic individuals may not be sufficiently motivated to adhere to a strict gluten-free diet. There may also be adverse psychological effects when asymptomatic individuals receive a diagnosis of a chronic incurable condition that demands substantial lifestyle changes.

For these reasons, widespread screening of asymptomatic individuals is not generally advocated at this time, even in populations in which the prevalence of celiac disease is high. This must be distinguished from testing to diagnose celiac disease in patients with subtle clinical manifestations in which instance the value of serologic tests as diagnostic aids is widely accepted.

**OTHER NONINVASIVE TESTS FOR THE DIAGNOSIS OF CELIAC DISEASE** — A variety of hematologic and biochemical abnormalities may be found in individuals with untreated celiac disease including iron deficiency, [folic acid](#) deficiency, and vitamin D deficiency. These abnormalities reflect nutritional deficiency states secondary to enteropathy-induced malabsorption. Although relevant to patient evaluation and management, none is sufficiently sensitive or specific to serve as useful screening or diagnostic tools [42]. An oral xylose and/or [lactulose](#) absorption test, fecal fat evaluation, small bowel radiographic study, or capsule endoscopy may also be abnormal in untreated celiac disease, but will not provide a specific diagnosis [61].

HLA typing may be useful in patients who are already on a gluten-free diet without having achieved a firm diagnosis. Those without HLA DQ2 or DQ8 are very unlikely to have celiac disease [62]. A systematic review of the literature estimated that testing for these haplotypes had a sensitivity of 90 to 95 percent but specificity was only around 30 percent [1]. Thus, the greatest value lies in its negative predictive value (ie, the disease is unlikely in those with a negative result). (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults"](#).)

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See ["Patient information: Celiac disease in children"](#) and ["Patient information: Celiac disease in adults"](#).) We encourage you to print or e-mail these topics, or to refer patients to our public web site, [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes these and other topics.

**SUMMARY AND RECOMMENDATIONS** — An approach to diagnosis of celiac disease is summarized in the following algorithm ([algorithm 1](#)). All testing should be performed while patients are on a gluten-containing diet.

IgA deficiency is more common in celiac disease (2 to 5 percent) than in the

general population (<0.5 percent). The IgA EMA and IgA tTG serology tests will be falsely negative in untreated celiac disease in patients with IgA deficiency. As a result, total serum IgA can be measured in addition to IgA EMA or IgA tTG especially when there is heightened clinical suspicion for celiac disease and IgA markers are negative. If total IgA levels are abnormally low, an IgG-based assay should be used to test for celiac disease. The IgG antigliadin assay has been traditionally used in this circumstance but is not ideal since it yields frequent false positive results. Thus, serum IgG tTG or IgG DGP tests are preferable. Negative results upon testing for HLA DQ2 or DQ8 can also help exclude the diagnosis in this setting.

In addition to serologic markers, the diagnosis usually requires a small bowel biopsy, which can be obtained during upper endoscopy. Exceptions are patients with compatible serologic findings and biopsy-proven dermatitis herpetiformis in whom the diagnosis can be established without a small bowel biopsy.

A hallmark on histology is the presence of villous atrophy. However, villous atrophy can be patchy, and may also be present in a variety of other disorders that should be considered in appropriate clinical settings ([table 1](#)) [63]. Several biopsies in the second and third portion of the duodenum (a minimum of four) should be obtained to maximize the likelihood of detecting villous atrophy. The accuracy of biopsies can be improved with staining techniques and magnification endoscopy; however, these approaches are not used routinely. (See "[Magnification endoscopy](#)".)

A few controversies remain regarding confirmation of the diagnosis. Some authorities recommend that a repeat small intestinal biopsy should be obtained 6 to 24 months after beginning a gluten-free diet to demonstrate histologic improvement. Some also recommended a repeat small bowel biopsy (after a gluten rechallenge) following a gluten-free diet. We do not believe that these approaches are generally required unless the diagnosis remains uncertain based upon the serologic profile, histology and clinical response. Furthermore, these approaches are not recommended in a consensus statement issued by the NIH [64]. (See "[Management of celiac disease in adults](#)".)

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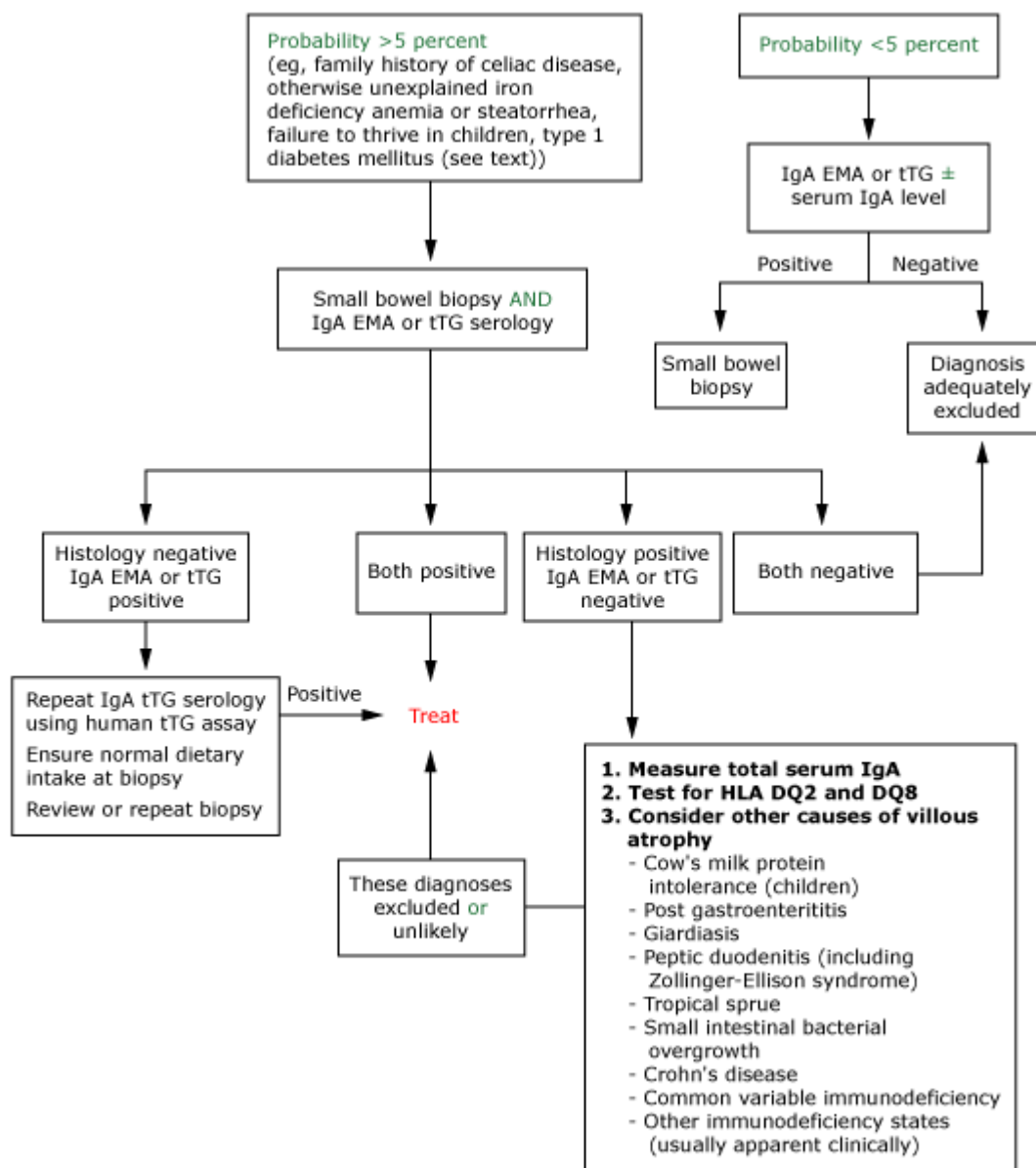
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## GRAPHICS

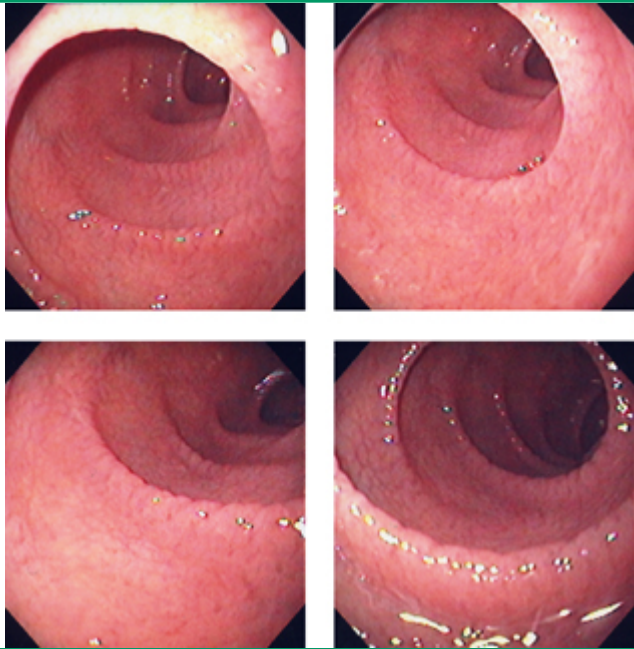
### Diagnosis of celiac disease



EMA: antiendomysial antibodies; tTG: tissue transglutaminase.

## Celiac disease

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Scalloped duodenal folds seen on endoscopy in a patient with celiac disease. *Courtesy of Eric D Libby, MD.*

## Causes of small intestinal villous atrophy other than celiac disease

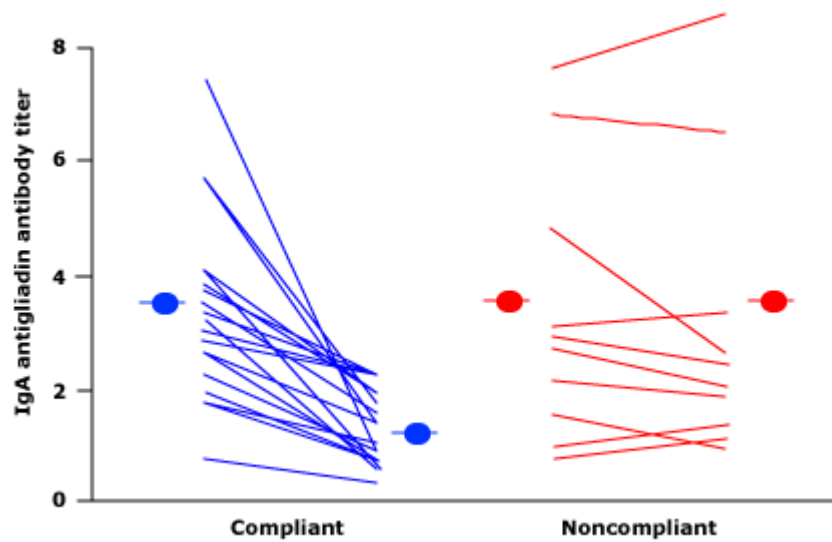
Bacterial overgrowth
Crohn's disease
Cow's milk protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Lymphoma
Peptic duodenitis
Post gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically)

## Definitions of sensitivity, specificity, and positive and negative predictive values

	Disease present	Disease absent
Test positive	A	B
Test negative	C	D
Sensitivity = $A \div (A + C)$		
Specificity = $D \div (B + D)$		
Positive predictive value = $A \div (A + B)$		
Negative predictive value = $D \div (C + D)$		

## Gluten-free diet lowers IgA antigliadin antibody titers in celiac disease

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Serum IgA antigliadin antibody titers (and the mean values) at diagnosis and after dietary therapy for 12 to 16 months with a gluten-free diet in compliant (n=20) and noncompliant (n=10) patients with celiac disease. Antibody titers fell significantly in the compliant group but not in those who were noncompliant.







## Management of celiac disease in children

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**INTRODUCTION** — Celiac disease is a condition in which there is abnormal small intestinal mucosa that improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. The disorder is commonly referred to as "celiac sprue" or "gluten-sensitive enteropathy" in the United States. It was first described by Samuel Gee in 1887 in a report entitled "On the Coeliac Affection," although a similar description of a chronic malabsorptive disorder by Aretaeus from Cappadocia (now Turkey) was recorded as far back as the second century AD [[1](#)].

The six key elements in the management of patients with celiac disease can be summarized with the following acronym [[2](#)]:

- Consultation with a skilled dietitian
- Education about the disease
- Lifelong adherence to a gluten-free diet
- Identification and treatment of nutritional deficiencies
- Access to an advocacy group
- Continuous long-term follow-up by a multidisciplinary team

Treatment of the patient with celiac disease begins with dietary counseling. Other issues that need to be considered include addressing nutritional needs (including the prevention of bone loss), monitoring of the response, and evaluating patients who do not respond.

The management of celiac disease and its complications are reviewed here. Its pathogenesis, clinical manifestations, and diagnosis are discussed separately. This topic is also discussed in an official position statement issued by the American Gastroenterological Association [[3](#)]. The discussion below reflects a 2004 consensus statement issued by the National Institutes of Health [[2](#)] and guidelines developed by the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) [[4](#)]. The pediatric guidelines are also available on the

NASPGHAN Web site ([www.naspgghan.org](http://www.naspgghan.org)). (See "[Clinical manifestations and diagnosis of celiac disease in children](#)" and "[Diagnosis of celiac disease](#)".)

## WHOM TO TREAT

**Presumptive celiac disease** — Treatment with a gluten-free diet is recommended for both diagnostic and therapeutic purposes for all children in one of the following groups:

- Children with characteristic findings on intestinal biopsy and symptoms consistent with celiac disease (including nonspecific symptoms such as constipation or abdominal pain).
- Children with characteristic findings on intestinal biopsy and belonging to a high-risk group (eg, relatives of patients with established celiac disease, or patients with type 1 diabetes), whether or not there are associated symptoms ([table 1](#)).
- Patients with dermatitis herpetiformis confirmed by skin biopsy, with or without associated pathology of the small intestinal mucosa.

Treatment with a gluten-free diet improves gastrointestinal symptoms as well as most of the non-gastrointestinal symptoms of celiac disease, and may reduce the risk of gastrointestinal malignancies, infertility, and low-birthweight offspring. (See "[Clinical manifestations and diagnosis of celiac disease in children](#)".)

**Latent/potential celiac disease** — Patients who are diagnosed with gluten sensitivity by a positive tissue transglutaminase or IgA endomysial antibody, but who have a normal small bowel biopsy, are considered to have latent or potential celiac disease. Such patients are currently not advised to be on a gluten-free diet but should continue to be monitored and rebiopsied if symptoms develop.

Before considering a patient to have latent celiac disease, it is important to make sure that the intestinal biopsies were adequate. The histologic abnormalities of celiac disease can be patchy, so multiple biopsies must be taken from the distal duodenum, and these should be evaluated by an expert pathologist [5]. In addition, we generally perform further serological testing using a second specific antibody (eg, antiendomysial antibodies). HLA testing may also be helpful; if the patient has neither the DQ2 nor DQ8 genotype, the likelihood of having celiac disease is very low. Because a child may not effectively communicate about symptoms that may herald active disease, periodic reevaluation for symptoms and growth is important, and an additional endoscopy with biopsies should be performed when appropriate in high-risk patients.

**PRINCIPLES OF A GLUTEN-FREE DIET** — The cornerstone of treatment of celiac

disease is the elimination of gluten in the diet. The principle sources of dietary gluten are wheat, rye, and barley. The toxicity of oats in celiac disease is now in doubt. (See ['Oats'](#) below.)

**Cereal chemistry** — Much work has been undertaken to characterize the toxic cereal fraction within wheat flour that is associated with celiac disease. The term gluten is used to describe the protein fraction of wheat flour, often referred to as prolamins due to the high content of the amino acids proline and glutamine. Gluten can be divided into an alcohol-soluble fraction, gliadin, and an alcohol-insoluble fraction, glutenin. Prolamins from other cereals are secalins from rye and hordeins from barley. The term gluten is often used loosely to refer to all prolamins found in wheat, rye, and barley.

The taxonomic relationship between the major cereal grains provides a framework upon which their toxicity in celiac disease can be predicted ([figure 1](#)). As an example, wheat, rye, and barley belong to the tribe known as Triticeae, while oats belong to a neighboring tribe (Aveneae). Thus, avenin (the major prolamins in oats) is genetically less similar to gluten than gluten is to secalin and hordein. However, despite the greater genetic difference, the prolamins from oats, barley, wheat, and rye have immunologic crossreactivity, reflecting their common ancestry [[6,7](#)].

The biochemistry of gluten proteins and the antibodies that are raised against them are discussed in detail separately. (See ["Management of celiac disease in adults", section on 'Cereal chemistry'](#) and ["Clinical manifestations and diagnosis of celiac disease in children", section on 'How to test'](#).)

**Oats** — Gluten, secalins, and hordeins are toxic to patients with celiac disease. The toxicity of oats is less clear because some studies suggest that pure oat flour can be tolerated without disease recurrence [[8-11](#)]. Oats contain a sequence homology (ie, QQQPF) with gliadin peptides, which have been shown to be disease-activating [[12,13](#)]. However, this homology may not be relevant since T-cell activation requires larger epitopes; in addition, oats contain a relatively smaller proportion of this toxic prolamins moiety compared with other gluten-containing cereals. Indeed, some studies suggest that tolerance to oats depends at least in part on the total amount consumed [[14](#)]. Daily oats consumption less than 40 to 60 g/day by patients whose celiac disease is in remission appears to be well tolerated, while larger daily intake is associated with disease recurrence [[14](#)].

Several randomized studies in adults suggest that oats caused no differences in nutritional status, symptoms, or laboratory or histologic measures after one or five years [[8,15,16](#)]. However, in another study, patients consuming oats had significantly more gastrointestinal symptoms (including diarrhea and constipation) and had a significantly higher density of intraepithelial lymphocytes [[17](#)]. A metaanalysis of 10 studies concluded that there is no good evidence that

consumption of oats causes mucosal damage in patients with celiac disease [18]. Among 165 patients included in the study, only one developed histological changes.

Few studies have addressed the safety of oats in children with celiac disease. One small open-label study suggested that oats may be safe [19]. A larger controlled trial randomly assigned 116 children with newly diagnosed celiac disease to a standard gluten-free diet, or a gluten-free diet in which additional wheat-free oat products were permitted [20]. Median daily oat intake was 16 g. All patients were in clinical remission at the end of the study (one year). There were no significant differences in clinical, histologic, or biochemical markers of disease activity.

Despite these observations, the long-term safety of oat consumption in patients with celiac disease is uncertain, and most studies that examined the safety of oats have included patients with relatively mild disease or whose disease was in remission upon reinstitution of oats in the diet. Furthermore, some patients may be exquisitely sensitive to oat prolamins. Thus, at the present time, a reasonable approach is to limit oat consumption to 50 to 60 g/day (approximately 2 oz) in patients with mild disease upon presentation or whose disease is in remission after a stringent gluten-free diet. The patients should be followed carefully for clinical or serologic evidence of disease recurrence after reintroducing oats. Patients with severe disease should probably avoid oats altogether. Oats also should be avoided if the purity cannot be guaranteed, as contamination with even small amounts of other cereals can cause damage to the intestinal tract [21].

## **NUTRITIONAL CONSIDERATIONS**

**Dietary counseling** — Consumption of a gluten-free diet requires a major lifestyle change since gluten is contained in a variety of foods that are commonly consumed in a Western diet. Thus, it is helpful to provide written information and dietary counseling to improve compliance. A number of resources are available for patients with celiac disease including a variety of cookbooks, gluten-free prepared foods, and Internet sites ([www.csaceliacs.org](http://www.csaceliacs.org) and [www.celiac.com](http://www.celiac.com)). (See "[Patient information: Celiac disease in adults](#)".)

As general rules, the following advice can be given to all patients:

- Foods containing wheat, rye, and barley should be avoided.
- Soybean or tapioca flours, rice, corn, buckwheat, and potatoes are safe.
- Read labels on prepared foods and condiments carefully, paying particular attention to additives such as stabilizers or emulsifiers that may contain gluten.
- Dairy products should be avoided initially since many patients with celiac disease have secondary lactose intolerance. Most children will tolerate lactose after mucosal healing. (See "[Lactose intolerance](#)".)

- Advice regarding consumption of oats is discussed above. (See ['Oats'](#) above.)

There is some disagreement over the strict definition and product labeling of gluten-free foods. Currently, foods must contain no more than 20 ppm gluten to be considered gluten-free [\[4\]](#).

**Is strict gluten avoidance necessary?** — Because gluten elimination poses several lifestyle restrictions, many patients ask whether small to moderate amounts of gluten in the diet are permissible. Furthermore, some patients consider symptoms to be sufficiently mild so as not to warrant the sacrifice of fastidiously avoiding gluten-containing foods. The problem is even greater among asymptomatic patients in whom celiac disease was diagnosed based upon antibody screening. The benefit of rigid gluten avoidance has not been proven since the natural history of celiac disease in such patients is unclear.

Several arguments favor encouraging strict adherence to a gluten-free diet in most patients with established celiac disease regardless of clinical symptoms:

- Despite feeling clinically well, patients may have a variety of micronutrient deficiencies that may ultimately have clinical sequelae (such as bone loss due to vitamin D deficiency) [\[22\]](#). (See below).
- Multiple reports have suggested increased overall mortality (mostly from gastrointestinal malignancies) in patients with celiac disease compared to the general population [\[23-25\]](#). Several studies have suggested the risk is decreased in patients adhering to a gluten-free diet [\[26-29\]](#). (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults"](#).)
- The likelihood that patients with celiac disease will develop other autoimmune disorders that have been associated with celiac disease (such as type 1 diabetes mellitus, connective tissue diseases, Hashimoto's thyroiditis, and Graves' disease) appeared to be related to the duration of exposure to gluten in at least one study [\[30\]](#), but a causal relation has not been established. (See ["Clinical manifestations and diagnosis of celiac disease in children", section on 'Diabetes mellitus'](#).)
- Mothers with untreated celiac disease are at increased risk for having low birth weight newborns and preterm births [\[31,32\]](#).

Although the benefit of rigid gluten avoidance has not been proven, the above considerations lead us to recommend a strict gluten-free diet for any patients with established celiac disease, even if small amounts of gluten do not cause symptoms. A review of the literature by an expert panel concluded that the lower threshold of gliadin intake that causes mucosal damage is between 10 and 100 mg [\[33\]](#).

**Micronutrient deficiencies** — An individual patient's overall nutritional status should be considered so that nutritional and caloric deficiencies can be adequately supplemented. Specific dietary deficiency such as iron, [folic acid](#), calcium, vitamin D, and, rarely, vitamin B12 deficiency should be corrected. A gluten-free diet may induce troublesome constipation since it is low in roughage. This usually responds to the addition of dietary rice bran and ispaghula husks; [psyllium](#) fiber or [methylcellulose](#) supplements are also generally gluten-free. (See "[Overview of the treatment of malabsorption](#)".)

**Prevention of bone loss** — Bone loss (principally osteopenia and less often osteoporosis) is common in celiac disease, and can occur in patients without gastrointestinal symptoms [[22,34-36](#)]. Much of the bone loss is related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency. (See "[Clinical manifestations and diagnosis of celiac disease in children](#)".)

Children with celiac disease have reduced bone mass at the time of diagnosis, similar to adults with newly diagnosed celiac disease. However, children are more likely than adults to have fully restored bone mass after 6 to 12 months of a gluten-free diet [[37-39](#)]. Therefore, the AGA guidelines suggest that DEXA scans are unnecessary in children with newly diagnosed uncomplicated celiac disease.

Recommendations for the prevention and treatment of osteoporosis in patients with celiac disease also have been proposed by the British Society of Gastroenterology [[40](#)]. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".) The American Gastroenterological Association (AGA) guideline for osteoporosis in gastrointestinal diseases [[41](#)], as well as other AGA guidelines, can be accessed through the AGA Web site at <http://www.gastro.org/practice/medical-position-statements>.

**MONITORING THE RESPONSE TO A GLUTEN-FREE DIET** — The rapidity of the response to a gluten-free diet is variable. Approximately 70 percent of patients have noticeable clinical improvement within two weeks [[42](#)]. As a general rule, symptoms improve faster than histology, especially when biopsies are obtained in the proximal intestine. The reason is incompletely understood; however, a likely explanation is that the less severely damaged distal small intestine recovers faster than the proximal intestine, which typically is affected more severely because of relatively increased exposure to gluten [[43](#)].

**Antibody testing** — We suggest measurement of celiac-specific antibodies (tissue

transglutaminase or antiendomysial antibodies) about six months after beginning a gluten-free diet. A decrease in the antibody titer, with eventual disappearance in most individuals, is an indirect indicator of dietary adherence and recovery. We also measure antibodies in children with persistent or recurrent symptoms at any time after starting a gluten-free diet. A rise in antibody levels may indicate that the individual is knowingly or inadvertently ingesting gluten again, and should prompt careful review of the diet. If patients remain asymptomatic, we measure antibodies annually to monitor adherence to the gluten-free diet.

**Biopsy** — The need for a follow-up biopsy in patients with clinical improvement has been debated, especially since serologic testing can be used to monitor recovery and compliance with the diet. (See "[Diagnosis of celiac disease](#)".) We suggest NOT repeating a biopsy in patients with a definite diagnosis of celiac disease who have all of the following characteristics:

- Symptoms suggestive of celiac disease and elevated tissue transglutaminase, or anti-endomysial antibodies at presentation.
- Initial intestinal biopsy with histologic changes characteristic of celiac disease (Marsh type 3 villous atrophy).
- Resolution of symptoms and marked decrease in tissue transglutaminase antibodies on a gluten-free diet.

This recommendation is consistent with NASPGHAN guidelines [4].

For children in whom the diagnosis is less certain because they do not meet one or more of the above characteristics, we suggest a second small intestinal biopsy 9 to 12 months after beginning a gluten-free diet to demonstrate histologic improvement. Although histologic improvement is usually seen by this time, persistent abnormalities have been described, even in patients with symptomatic improvement [44,45]. The significance is at the moment unclear, but in many cases the abnormalities do not appear to be linked with dietary problems. After checking for dietary non-compliance or inadvertent ingestion of gluten, other causes of villous atrophy should be considered in these patients. (See '[Patients with other disorders](#)' below.)

**Gluten rechallenge** — Gluten rechallenge (a traditional approach to diagnosis of celiac disease) is generally not required unless the diagnosis remains uncertain. Guidelines issued by the European Society of Paediatric Gastroenterology and Nutrition suggested that gluten rechallenge is not mandatory in patients with good improvement in symptoms, histology, and a decline in the titer of antiendomysial antibodies (which usually return to normal in three to six months) [46]. Gluten rechallenge was also considered to be unnecessary in consensus statements issued by the National Institutes of Health [2] and NASPGHAN [4]. (See "[Diagnosis of celiac disease](#)".)



Furthermore, a rare hazard in giving a gluten rechallenge is the development of fulminant diarrhea, with resulting dehydration, acidosis, and other metabolic disturbances (a condition known as "gliadin shock") [47]. Such patients should be treated with corticosteroids.

When gluten rechallenge is chosen for patients in whom the diagnosis remains uncertain, the patient is asked to ingest at least 10 g of gluten per day (an amount contained in four slices of regular bread) for four to six weeks, followed by endoscopic biopsies. The biopsy date should be advanced in patients who develop severe symptoms.

**PNEUMOCOCCAL VACCINATION** — Celiac disease is associated with hyposplenism. As a result, children with celiac disease should be immunized with a pneumococcal vaccine. In the United States, most children are immunized during infancy with the conjugate vaccine. Like other children who are at increased risk for invasive pneumococcal disease, children with celiac disease should receive an additional series of polysaccharide vaccine as appropriate for their age [48,49]. (See "[Clinical manifestations and diagnosis of celiac disease in children](#)" and "[Pneumococcal \(\*Streptococcus pneumoniae\*\) conjugate vaccines in children](#)".)

**NONRESPONDERS** — The majority of patients with celiac disease respond to a gluten-free diet. The most common reasons for a lack of response are poor compliance or inadvertent gluten ingestion ([table 2](#)). Thus, a meticulous dietary history should be obtained, and dietary counseling pursued with an experienced dietitian in patients who continue to have symptoms or persistent histologic abnormalities, or in those in whom serum antibody titers have not declined.

Trace amounts of gluten may be contained in products that are labeled as gluten-free. However, the small amount of gluten contained in these products does not necessarily translate into refractory disease. A study evaluating occult gluten intake (from grain contaminants) among 76 patients on a gluten-free diet estimated that gluten contamination of up to 100 parts per million (up to a total of 30 mg per day) did not result in histologic injury [50]. Interestingly, 13 of 59 naturally gluten-free products and 11 of 24 wheat starch-based gluten-free products contained gluten ranging from 20 to 200 mg/kg. Medications (pills) generally contain minimal gluten and do not need to be avoided.

Patients who do not respond despite adherence to a gluten-free diet fall into three main categories:

- Patients with clinical or histologic features that are caused by other disorders
- Patients with refractory sprue
- Patients with ulcerative jejunitis or intestinal lymphoma (see "[Clinical manifestations, pathologic features, and diagnosis of enteropathy-associated](#)")

### T-cell lymphoma")

Another consideration in incomplete responders or nonresponders is that not all clinical features of celiac disease respond at the same rate. Furthermore, bone loss caused by secondary hyperparathyroidism and peripheral neuropathy may improve only partially despite a gluten-free diet [37]. (See '[Dermatitis herpetiformis](#)' below and '[Clinical manifestations and diagnosis of celiac disease in children](#)'.)

**Patients with other disorders** — Other diagnoses should be considered in patients who, despite apparent compliance, continue to have symptoms or do not have histologic improvement.

- As mentioned above, concomitant or secondary lactose intolerance is a possible cause of continued diarrhea and flatulence. (See '[Lactose intolerance](#)'.)
- Patients with celiac disease are susceptible to common bowel disturbances such as irritable bowel syndrome, which affects a large proportion of the general population and may present with features suggestive of malabsorption. (See '[Clinical manifestations and diagnosis of irritable bowel syndrome](#)' and '[Clinical features and diagnosis of malabsorption](#)'.)
- A small percentage of patients develop small bowel bacterial overgrowth, which may respond to antibiotics [51]. (See '[Treatment of small intestinal bacterial overgrowth](#)'.)
- A number of diseases associated with small bowel villous atrophy also should be excluded in patients with persistent symptoms who do not show histologic improvement ([table 3](#)) [52]. (See '[Clinical features and diagnosis of malabsorption](#)'.)

**Refractory sprue** — Refractory sprue (also referred to as "unclassified sprue") occurs almost exclusively in adults. These patients fall into two clinical categories [53]:

- Patients who have no initial response to a gluten-free diet
- Patients who experience initial clinical improvement on a gluten-free diet, but, after a period of remission, develop disease refractory to gluten abstinence

Refractory sprue can be severe and associated with progressive malabsorption and death. A subset of patients develop subepithelial collagen deposition, a condition referred to as "collagenous sprue" [54]. The diagnostic workup and management of patients with refractory sprue is discussed in detail separately. (See '[Management of celiac disease in adults](#)', section on 'Refractory sprue'.)

**DERMATITIS HERPETIFORMIS** — Celiac disease is associated with a number of

skin disorders of which dermatitis herpetiformis is the most common ([table 4](#)) [[55](#)]. Dermatitis herpetiformis is characterized by an itchy papular vesicular eruption usually located symmetrically on the elbows, knees, buttocks, sacrum, face, neck, trunk and occasionally within the mouth ([picture 1A-B](#)). The predominant symptoms are itching and burning that are rapidly relieved with rupture of the blisters. (See "[Clinical manifestations and diagnosis of celiac disease in children](#)", [section on 'Dermatitis herpetiformis'](#) and "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".)

Improvement in dermatitis herpetiformis following withdrawal of gluten may be considerably delayed (6 to 12 months) compared to the response of the intestinal manifestations of the disease [[56](#)]. As a result, treatment usually includes medical therapy (such as [dapsone](#)) in addition to gluten avoidance [[55](#)].

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "[Patient information: Celiac disease in children](#)".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

**SUMMARY AND RECOMMENDATIONS** — Celiac disease is a genetically determined sensitivity to dietary gluten, which causes intestinal inflammation and loss of villous surface area.

## Treatment

- Patients with serologically and histologically confirmed celiac disease and compatible clinical or laboratory manifestations should adhere to a gluten-free diet. For patients with symptoms, we recommend strict avoidance of gluten ([Grade 1A](#)). For patients with few or no symptoms, but with histologic evidence of celiac disease, we also suggest strict gluten avoidance ([Grade 2C](#)). This suggestion recognizes there are no controlled trials examining the long-term effects of a gluten-free diet in asymptomatic patients, or comparing a low-gluten diet to a gluten-free diet, and that quality of life may be adversely affected by the dietary regimen. The diet should be guided by in-depth consultation with an expert dietitian. (See "[Is strict gluten avoidance necessary?](#)" above.)
- A gluten-free diet requires strict avoidance of wheat, rye, and barley. Whether oat products can be safely included in a gluten-free diet is controversial. For patients with disease that is mild or in remission, we suggest limiting oat consumption to 50 to 60 g/day (approximately 2 oz) ([Grade 2C](#)). These patients should be followed carefully for clinical or serologic evidence of disease recurrence after reintroducing oats. For patients with severe disease, we suggest avoiding oats altogether ([Grade 2C](#)). (See "[Oats](#)" above.)

- Patients with positive tests for tissue transglutaminase or anti-endomysial antibodies, but normal results of small bowel biopsies, are considered to have "latent" or "potential" celiac disease. We suggest NOT treating such patients with a gluten-free diet (**Grade 2C**). However, it is important that histologically evident celiac disease was adequately evaluated in such patients with multiple intestinal biopsies since the histologic abnormalities can be patchy. These patients should be carefully monitored for growth failure and other symptoms that might suggest active celiac disease, and should be rebiopsied if symptoms develop (see '[Latent/potential celiac disease](#)' above).
- Celiac disease is associated with hyposplenism. We suggest that patients with celiac disease receive pneumococcal vaccine as indicated for other patients with increased risk for invasive pneumococcal disease (**Grade 2C**). (See '[Pneumococcal vaccination](#)' above.)

## Monitoring

We use the following approach to monitor a patient with celiac disease after establishment of a gluten-free diet, as outlined in the NASPGHAN guidelines. (See '[Monitoring the response to a gluten-free diet](#)' above.)

- Specific serologic testing should be repeated after six months on a gluten-free diet. A decrease in the antibody titer indicates adherence to the diet and supports the diagnosis of celiac disease. (See '[Antibody testing](#)' above.)
- When patients present with typical symptoms, have characteristic laboratory and histological findings, and respond well to a gluten-free diet, as measured by symptoms and antibodies, the diagnosis of celiac disease is clearly established. For these patients, we do not repeat the duodenal biopsy after beginning a gluten-free diet. (See '[Biopsy](#)' above.)
- For patients who do not meet all of the criteria above, the diagnosis of celiac disease is less firmly established. For these patients, we generally perform a second biopsy after 9 to 12 months of a strict gluten-free diet. (See '[Biopsy](#)' above.)
- Rechallenging the patient with gluten is no longer required to establish a diagnosis of celiac disease. However, gluten rechallenge may be helpful for selected patients in whom the diagnosis remains ambiguous after a trial of a gluten-free diet. (See '[Gluten rechallenge](#)' above.)
- The majority of patients with celiac disease respond to a gluten-free diet. The most common reasons for lack of response are poor compliance or inadvertent gluten ingestion ([table 2](#)). All patients with celiac disease should be

reevaluated periodically. The evaluation should include assessment of growth, gastrointestinal and other symptoms associated with celiac disease, and the patient's understanding of and compliance with the gluten-free diet. We measure tissue transglutaminase or other specific antibodies annually, and in patients with persistent or recurrent symptoms. (See '[Monitoring the response to a gluten-free diet](#)' above.)

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## GRAPHICS

### Prevalence of celiac disease in special populations

	Percent of group affected	Fold increase in risk as compared to general population
General population (US and Europe) <sup>[1]</sup>	0.7 to 1.0	-
Relatives of patient with celiac disease <sup>[1,2]</sup>		
first-degree relatives	4 to 5	6
second degree relatives	3	3
Down syndrome <sup>[2,3]</sup>	5 to 16	7 to 21
Type 1 diabetes <sup>[2,4]</sup>	5 to 10	7 to 13
IgA deficiency <sup>[2,5]</sup>	2 to 8	3 to 11
Williams syndrome <sup>[6]</sup>	8	11
Turner syndrome <sup>[2]</sup>	4 to 8	5 to 11
Autoimmune thyroid disease <sup>[7]</sup>	4.5	6 (less in children)

Data from:

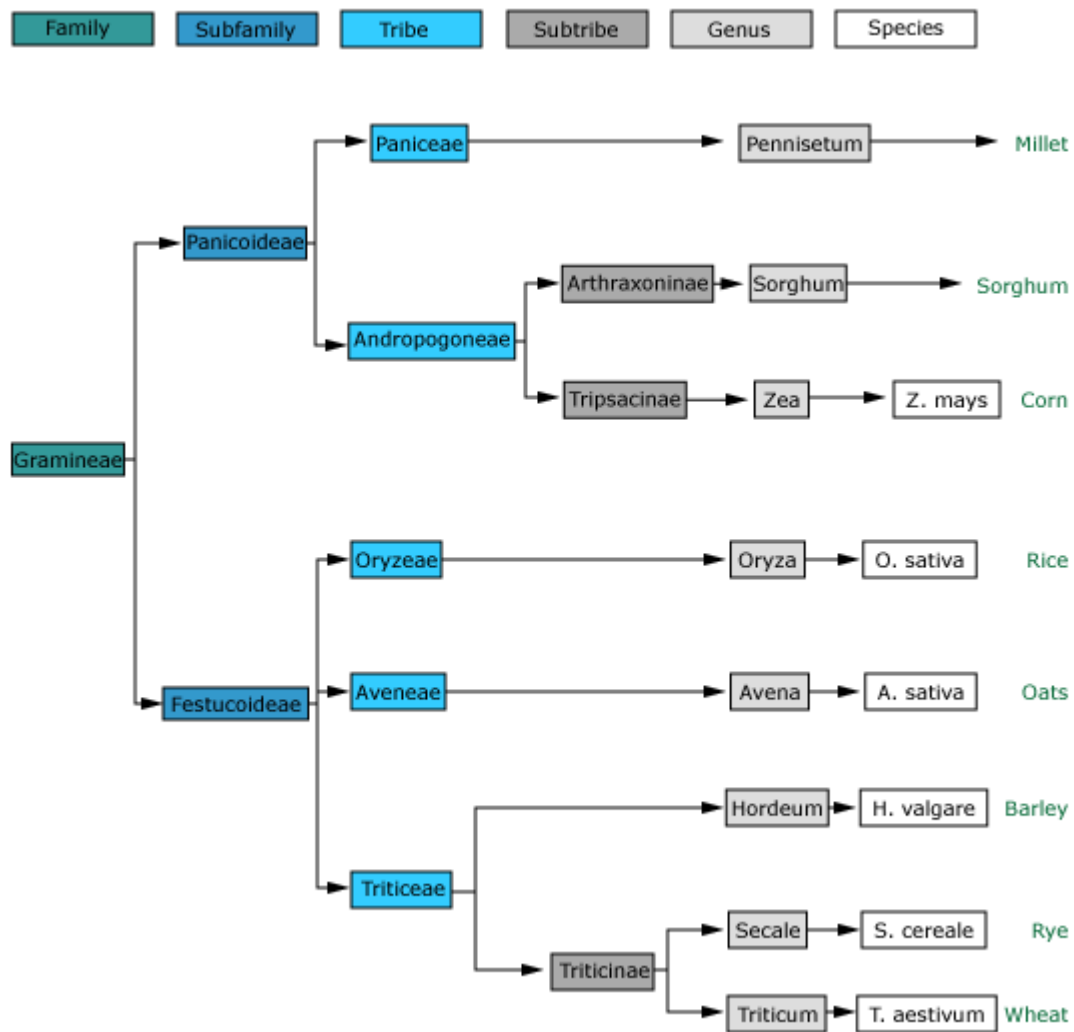
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## Taxonomic relationships of major cereal grains



Adapted from Kasarda, DD, *Proc Natl Acad Sci U S A* 1984; 81:4712.

## Foods and products that may contain gluten

Frequently overlooked foods that may contain gluten and need to be verified:	NOT ALLOWED in any form:
Brown rice syrup	Wheat (einkorn, durum, faro, graham, kamut, semolina, spelt)  Rye  Barley  Triticale  Malt, malt flavoring, malt vinegar (are generally made from barley, verify the source)
Breeding and coating mixes	
Croutons	
Energy bars	
Flour or cereal products	
Imitation bacon	
Imitation seafood	
Marinades	
Panko (Japanese bread crumbs)	
Pastas	
Processed luncheon meats	
Sauces, gravies	
Self-basting poultry	
Soy sauce or soy sauce solids	
Soup bases	
Stuffings, dressing	
Thickeners (roux)	
Communion wafers	
Herbal supplements	
Drugs and over-the-counter medications	
Nutritional supplements	
Vitamins and mineral supplements	

Play-dough, crayons, paint, glue, paper mache:  
A potential problem if the child puts their hands  
on or in the mouth while playing. Wash hands  
after using these products.

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*Reprinted with permission: "Frequently overlooked foods that may contain gluten and need to be verified." From Quick Start Diet Guide for Celiac Disease © 2009. Celiac Disease Foundation. [www.celiac.org](http://www.celiac.org).*

## Causes of small intestinal villous atrophy other than celiac disease

Bacterial overgrowth
Crohn's disease
Cow's milk protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Lymphoma
Peptic duodenitis
Post gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically)

## Skin disorders associated with celiac disease

Acquired ichthyosis
Cutaneous amyloid
Cutaneous vasculitis
Dermatitis herpetiformis
Eczema
Epidermal necrolysis
Nodular prurigo
Pityriasis rubra pilaris
Pustular dermatitis

## Dermatitis herpetiformis

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A skin blister on the elbow of a subject with dermatitis herpetiformis. *Reproduced with permission from the American Gastroenterological Association. Ciclitira, PJ. Gastroenterology 2001; 120:1526.*



## Dermatitis herpetiformis



Herpetiform clusters of vesicles on an erythematous, edematous base with crusts and postinflammatory pigmentation on the upper back and shoulder. *Reproduced with permission from: Skin signs of immune, autoimmune, and rheumatic diseases. In: Color Atlas and Synopsis of Clinical Dermatology, 3rd ed, Fitzpatrick, TB, Johnson, RA, Wolff, K (Eds), McGraw-Hill, New York 1997. p.327. Copyright © 1997 McGraw Hill.*





## Management of celiac disease in adults

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**INTRODUCTION** — Celiac disease can be defined as a condition in which there is an abnormal small intestinal mucosa that improves morphologically when treated with a gluten-free diet and relapses when gluten is reintroduced. The disorder is commonly referred to as "celiac sprue" or "gluten-sensitive enteropathy" in the United States. It was first described by Samuel Gee in 1887 in a report entitled "On the Coeliac Affection," although a similar description of a chronic malabsorptive disorder by Aretaeus from Cappadocia (now Turkey) was recorded as far back as the second century AD [1].

As a general rule, there are six key elements in the management of patients with celiac disease, which can be summarized with the following acronym [2]:

- Consultation with a skilled dietitian
- Education about the disease
- Lifelong adherence to a gluten-free diet
- Identification and treatment of nutritional deficiencies
- Access to an advocacy group
- Continuous long-term follow-up by a multidisciplinary team

The management of celiac disease and its complications will be reviewed here. Its pathogenesis, clinical manifestations, and diagnosis are discussed separately. (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults"](#) and ["Diagnosis of celiac disease"](#).) The American Gastroenterological Association (AGA) guideline for the diagnosis and management of celiac disease [3], as well as other AGA guidelines, can be accessed through the AGA web site at [www.gastro.org/practice/medical-position-statements](http://www.gastro.org/practice/medical-position-statements). The discussion below also reflects a 2004 consensus statement issued by the National Institutes of Health [2].

**PRINCIPLES OF A GLUTEN-FREE DIET** — The cornerstone of treatment of celiac

disease is the elimination of gluten in the diet. The principal sources of dietary gluten are wheat, rye, and barley. Although gluten is also found in oats, the toxicity of oats in celiac disease is now in doubt (see '[Oats](#)' below).

**Cereal chemistry** — Much work has been undertaken to characterize the toxic cereal fraction within wheat flour that is associated with celiac disease. Wheat grains are composed of three major components, which are separated by milling: the outer husk (ie, bran), the germ, and the endosperm or white flour (which accounts for approximately 70 percent of the grain by weight).

The fraction of wheat that is responsible for celiac disease is known to be protein since gliadin (see below) that has been chemically processed to remove associated fat will induce the disease [\[4\]](#). Wheat protein exists in a number of storage forms, which can be categorized into four general groups based upon their solubility characteristics:

- Prolamins (soluble in ethanol)
- Glutenins (partially soluble in dilute acid or alkali solutions)
- Globulins (soluble in 10 percent NaCl)
- Minor albumins (soluble in water)

The term "gluten" encompasses the ethanol-soluble fraction (ie, prolamins) and the glutenins. The prolamins in wheat are referred to as gliadins. Prolamins from other cereals are also considered to be gluten, and are named according to their source (eg, secalins from rye, hordeins from barley, avenins from oats, and zeins from corn). Prolamins from corn are definitely non-toxic.

The taxonomic relationship between the major cereal grains provides a framework upon which their toxicity in celiac disease can be predicted ([figure 1](#)). As an example, wheat, rye, and barley belong to the tribe known as Triticeae, while oats belong to a neighboring tribe (Aveneae). Thus, avenin (the major prolamin in oats) is genetically less similar to gliadin than gliadin is to secalin and hordein. However, despite the greater genetic difference, the prolamins from oats, barley, wheat, and rye have immunologic crossreactivity, reflecting their common ancestry [\[5-7\]](#).

Gliadin can be separated into four major fractions (alpha, beta, gamma, and omega), based upon their electrophoretic mobility or their N-terminal amino acid sequences [\[8\]](#). All four fractions appear to be toxic to patients with celiac disease [\[9\]](#). A number of amino acid motifs within the subunits have been implicated in the pathogenesis of celiac disease, but a definitive understanding of the relationship between their structure and toxicity has not been achieved. A 33 amino acid peptide has been identified with several characteristics suggesting that it may be the dominant initiator of the inflammatory response [\[10\]](#). This peptide is particularly resistant to gastrointestinal peptidases but can be degraded by prolyl

bacterial endopeptidase. (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults", section on 'Serum autoantibodies'.](#))

It is possible that immunologic similarities between gliadin protein motifs and enteric pathogens may be involved in pathogenesis of an immunologic response to antigens in gluten. This hypothesis was supported in one study in which analysis of alpha gliadin demonstrated an amino acid region that was homologous to the 54KDa E1b protein coat of adenovirus 12, suggesting that exposure to the virus in a susceptible person could be involved in the pathogenesis of celiac disease [11]. (See ["Epidemiology and clinical manifestations of adenovirus infection".](#))

**Oats** — Gliadin, secalin, and hordeins are toxic to patients with celiac disease. As mentioned above, the toxicity of oats is less clear because some studies suggest that pure oat flour can be tolerated without disease recurrence [12-16]. In one study, for example, 52 adults with celiac disease in remission and 40 with newly diagnosed celiac disease were randomly assigned to a gluten-free diet without oats, or a gluten-free diet with a total daily consumption of 50 to 70 g of oats [12]. At the end of one year, no significant difference was observed in the nutritional status, symptoms, or laboratory or histologic measures between the two groups. After 6 to 12 months of follow-up, the rate of disappearance of gliadin and reticulic antibodies and the decrease in intraepithelial lymphocytes were similar in the two groups [17]. A follow-up report suggested that the ability to tolerate oats persisted for at least five years in the majority of patients [15].

Somewhat different conclusions were reached in another controlled trial involving 39 adults who were randomly assigned to either a gluten-free diet with 50 g of oat-containing products daily or to a gluten-free diet without oats for one year [18]. Quality of life scores were similar between the groups, and there were no significant differences in the villous structure of small bowel biopsies. However, patients consuming oats had significantly more gastrointestinal symptoms (including diarrhea and constipation) and had a significantly higher density of intraepithelial lymphocytes. The authors concluded that oats can provide an alternative in the gluten-free diet but that patients should be aware of the possible increase in symptoms.

Oats contain a sequence homology (ie, QQQPF) with gliadin peptides, which have been shown to be disease activating [19,20]. However, this homology may not be relevant since T-cell activation requires larger epitopes. Another possible explanation for why oats may be better tolerated is that oats contain a relatively smaller proportion of this toxic prolamins moiety compared with other gluten-containing cereals. This hypothesis is supported when collectively considering the studies on oat challenge in patients with celiac disease; these studies suggest that tolerance to oats depends at least in part upon the total amount consumed [21].

Daily oats consumption less than 40 to 60 g/day by patients whose celiac disease is in remission appears to be well tolerated, while larger daily intake is associated with disease recurrence [21]. However, studies using these larger quantities were performed before the advent of small bowel biopsy.

Despite these observations, the long-term safety of oat consumption in patients with celiac disease is uncertain, and most studies that examined the safety of oats have included patients with relatively mild disease or whose disease was in remission upon reinstitution of oats in the diet. Furthermore, some patients may be exquisitely sensitive to oat prolamins [22]. Thus, at the present time, a reasonable approach is to limit oat consumption to 50 to 60 g/day (approximately 2 oz) in patients with mild disease upon presentation or whose disease is in remission after a stringent gluten-free diet. The latter patients should be followed carefully for clinical or serologic evidence of disease recurrence after reintroducing oats. Patients with severe disease should probably avoid oats altogether, especially since oat products obtained in the store are frequently contaminated with small amounts of other cereals [23]. One study suggested that oats may be safe for consumption by children with celiac disease, although confirmation is required [24].

**TREATMENT** — Treatment of the patient with celiac disease begins with dietary counseling. Other issues that need to be considered include addressing nutritional needs (including the prevention of bone loss), monitoring of the response, and evaluating patients who do not respond.

**Dietary counseling** — Consumption of a gluten-free diet requires a major lifestyle change since gluten is contained in a variety of foods that are commonly consumed in a Western diet. Thus, it is usually helpful to provide written information and dietary counseling to improve compliance. A number of resources are available for patients with celiac disease including a variety of cookbooks, gluten-free prepared foods, and Internet sites: [www.csaceliacs.org](http://www.csaceliacs.org) and [www.celiac.com](http://www.celiac.com). (See "[Patient information: Celiac disease in adults](#)".)

As general rules, the following advice can be given to all patients:

- Foods containing wheat, rye, and barley should be avoided.
- Soybean or tapioca flours, rice, corn, buckwheat, and potatoes are safe.
- Read labels on prepared foods and condiments carefully, paying particular attention to additives such as stabilizers or emulsifiers that may contain gluten.
- Dairy products may not be well tolerated initially since many patients with celiac disease can have secondary lactose intolerance. (See "[Lactose intolerance](#)".) As a result, lactose-containing products should initially be avoided in patients whose symptoms appear to be worsened by them.
- Advice regarding consumption of oats is discussed above.

**Is strict gluten avoidance necessary?** — Because gluten elimination poses several lifestyle restrictions, many patients ask whether small to moderate amounts of gluten in the diet are permissible [25]. Furthermore, some patients consider symptoms to be sufficiently mild so as not to warrant the sacrifice of fastidiously avoiding gluten-containing foods. The problem is even greater among asymptomatic patients in whom celiac disease was diagnosed based upon antibody screening. The benefit of rigid gluten avoidance has not been proven since the natural history of celiac disease in such patients is unclear.

The ability to tolerate gluten in the diet is highly variable among patients. While some patients tolerate the reintroduction of small amounts of gluten in their diet after achieving remission, others are exquisitely sensitive to even small amounts. Despite this variable response, several arguments favor encouraging strict adherence to a gluten-free diet in most patients with established celiac disease regardless of clinical symptoms:

- Despite feeling clinically well, patients may have a variety of micronutrient deficiencies that may ultimately have clinical sequelae such as bone loss due to vitamin D deficiency (see '[Prevention of bone loss](#)' below) [26].
- Multiple reports have suggested increased overall mortality (mostly from gastrointestinal malignancies) in patients with celiac disease compared to the general population. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".) Several studies have suggested that the risk is decreased in patients adhering to a gluten-free diet [27-30].
- At least two studies found that the likelihood that patients with celiac disease will develop other autoimmune disorders associated with celiac disease (such as type 1 diabetes mellitus, connective tissue diseases, Hashimoto's thyroiditis, and Graves' disease) appeared to be related to the duration of exposure to gluten [31,32], although discordant data have been reported [33].
- Mothers with untreated celiac disease are at increased risk for having low birth weight newborns and preterm births [34,35].

At present, patients who are diagnosed with gluten sensitivity by a positive IgA endomysial antibody, but who have a normal small bowel biopsy, are considered to



be latent celiacs. Such patients are currently not advised to be on a gluten-free diet but should continue to be monitored and rebiopsied if symptoms develop. However, it is important that histologically evident celiac disease was adequately evaluated in such patients with multiple intestinal biopsies since the histologic abnormalities can be patchy [36].

**Nutritional considerations** — An individual patient's overall nutritional status should be considered so that nutritional and caloric deficiencies can be adequately supplemented. Specific dietary deficiency such as iron, [folic acid](#), calcium, vitamin D and, rarely, vitamin B12 deficiency should be corrected. (See "[Overview of the treatment of malabsorption](#)".) A gluten-free diet may induce troublesome constipation since it is low in roughage. This usually responds to fiber supplementation with [psyllium](#) seed husks.

**Prevention of bone loss** — Bone loss (principally osteopenia and less often osteoporosis) is common in celiac disease, and can occur in patients without gastrointestinal symptoms [26,37-39]. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".) Much of the bone loss is related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency. It can only be partially reversed with a gluten-free diet; loss of bone density in the peripheral skeleton may persist despite apparent normalization at axial skeletal sites [40]. Patients with advanced disease may have bone pain, pseudofractures, or deformity, but the majority of patients are asymptomatic or have only raised serum levels of alkaline phosphatase or hypocalcemia [26,41].

Patients diagnosed with celiac disease should be evaluated for bone loss using a DEXA (dual energy x-ray absorptiometry) scan. Monitoring by repeat DEXA scan after one year is useful in patients with osteopenia since it permits estimation of the rate of change of bone mineral density [42]. Treatment of osteoporosis and osteopenia is discussed in detail separately. (See "[Overview of the management of osteoporosis in postmenopausal women](#)" and "[Treatment of osteoporosis in men](#)".) It is also addressed in a guideline issued by the American Gastroenterological Association ([algorithm 1](#)). The AGA guideline for osteoporosis in gastrointestinal disease [43], as well as other AGA guidelines, can be accessed through the AGA web site at [www.gastro.org/practice/medical-position-statements](http://www.gastro.org/practice/medical-position-statements).

**Pneumococcal vaccination** — Celiac disease is associated with hyposplenism. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".) Thus, prophylactic administration of pneumococcal vaccine is reasonable. (See "[Pneumococcal vaccination in adults](#)".)

**Monitoring the response to a gluten-free diet** — The rapidity of the response to a gluten-free diet is variable. Approximately 70 percent of patients have noticeable clinical improvement within two weeks [44]. As a general rule,



symptoms improve faster than histology, especially when biopsies are obtained in the proximal intestine. The reason is incompletely understood; however, a possible explanation is that the less severely damaged distal small intestine recovers faster than the proximal intestine, which is typically more severely affected due to relatively increased exposure to gluten [45].

The need for a follow-up biopsy in patients with clinical improvement has been debated, especially since serologic testing can be used to monitor recovery and compliance with the diet. Some authorities rely on clinical improvement and changes in serologic markers, reserving re-biopsy for nonresponsive patients in whom there remains diagnostic uncertainty, or those who wish to confirm mucosal healing. (See "[Diagnosis of celiac disease](#)".)

We suggest that a repeat small intestinal biopsy be obtained three to four months after beginning a gluten-free diet to demonstrate histologic improvement. If improvement in small intestinal morphology is not seen, but symptomatic improvement has occurred, the diet should be continued and the small intestinal biopsy should be repeated after six to nine months. Although histological improvement is usually seen, persistent abnormalities have been described, even in patients with symptomatic improvement [46,47]. The significance is at the moment unclear, but the abnormalities do not appear to be linked with dietary problems. Other diagnoses, after a first check for non-compliance, or inadvertent ingestion of gluten should be considered in these patients (see '[Patients with other disorders](#)' below).

**Gluten rechallenge** — Gluten rechallenge (a traditional approach to diagnosis of celiac disease) is generally not recommended unless the diagnosis remains uncertain. The most convenient way to give a gluten challenge is to ask the patient to ingest at least 10 g of gluten per day (an amount contained in four slices of regular bread) and to perform a small bowel biopsy when celiac disease symptoms occur, or after two weeks in adults and six weeks (by convention) in children in the absence of such symptoms.

A guideline issued by the European Society of Paediatric Gastroenterology and Nutrition suggested that gluten rechallenge is not mandatory in patients with good improvement in symptoms, histology, and a decline in the titer of antiendomysial antibodies (which usually return to normal in three to six months) [48]. A more detailed discussion on the role of antibodies to measure response is available elsewhere. (See "[Diagnosis of celiac disease](#)".) Gluten rechallenge was also considered to be unnecessary in a consensus statement issued by the National Institutes of Health [2].

Furthermore, a rare hazard in giving a gluten rechallenge is the development of fulminant diarrhea, with resulting dehydration, acidosis, and other metabolic

disturbances (a condition known as "gliadin shock") [49]. Such patients should be treated with corticosteroids. There is a suggestion that use of gluten challenge in young children may be associated with an increased likelihood of development of autoimmune disorders such as IDDM [31].

**Nonresponders** — The majority of patients with celiac disease respond to a gluten-free diet. The most common reasons for a lack of response are poor compliance or inadvertent gluten ingestion ([table 1](#)) [50,51]. Thus, a meticulous dietary history should be obtained, and dietary counseling pursued with an experienced dietitian in patients who continue to have symptoms or persistent histologic abnormalities, or in those in whom serum antibody titers have not declined.

Trace amounts of gluten may be contained in products that are labeled as gluten-free. However, the small amount of gluten contained in these products does not necessarily translate into refractory disease. A study evaluating occult gluten intake (from grain contaminants) among 76 patients on a gluten-free diet estimated that gluten contamination of up to 100 parts per million (up to a total of 30 mg per day) did not result in histologic injury [52]. Interestingly, 13 of 59 naturally gluten-free products and 11 of 24 wheat starch-based gluten-free products contained gluten ranging from 20 to 200 mg/kg. Medications (pills) generally contain minimal gluten and do not need to be avoided. Information about gluten-free drugs is available at [www.glutenfreedugs.com](http://www.glutenfreedugs.com).

Patients who do not respond despite adherence to a gluten-free diet fall into three main categories:

- Patients with clinical or histologic features that are caused by other disorders
- Patients with refractory sprue
- Patients with ulcerative jejunitis or intestinal lymphoma

Another consideration in incomplete responders or nonresponders is that not all clinical features of celiac disease respond at the same rate (see '[Dermatitis herpetiformis](#)' below). Furthermore, bone loss due to secondary hyperparathyroidism and peripheral neuropathy may only improve partially despite a gluten-free diet [40]. (See "[Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults](#)".)

**Patients with other disorders** — Other diagnoses should be considered in patients who, despite apparent compliance, continue to have symptoms or do not have histologic improvement [50,53]. In a series of 78 patients with celiac disease treated with a gluten-free diet for at least 12 months, persistent diarrhea was observed in 13 patients (17 percent) [53].

Other diagnoses to consider in patients who do not respond to a gluten-free diet

include [53]:

- Concomitant or secondary lactose intolerance is a possible cause of continued diarrhea and flatulence. (See "[Lactose intolerance](#)".)
- Patients with celiac disease may have concurrent bowel disturbances such as irritable bowel syndrome, which affects a large proportion of the general population. (See "[Clinical manifestations and diagnosis of irritable bowel syndrome](#)".)
- Small bowel bacterial overgrowth, which may respond to antibiotics, develops in a small percentage of patients with celiac disease [54,55]. (See "[Treatment of small intestinal bacterial overgrowth](#)".)
- Diseases associated with small bowel villous atrophy should be excluded in patients with persistent symptoms who do not show histologic improvement (table 2) [56]. (See "[Clinical features and diagnosis of malabsorption](#)".)
- Some patients have coexisting pancreatic insufficiency [57]. (See "[Overview of the treatment of malabsorption](#)".)
- Microscopic colitis was found in 4 percent of 1009 patients with celiac disease, which represents a 70-fold increase in risk [58]. These patients had more severe villous atrophy and frequently required glucocorticoids or immunosuppressive drugs to treat the diarrhea. (See "[Lymphocytic and collagenous colitis \(microscopic colitis\)](#)".)

**Refractory sprue** — Patients with refractory sprue (also referred to as "unclassified sprue") fall into two clinical categories [59,60]:

- Patients who have no initial response to a gluten-free diet
- Patients who experience initial clinical improvement on a gluten-free diet, but, after a period of remission, develop disease refractory to gluten abstinence

Refractory sprue has also been subdivided into two immunologic categories [61-65]:

- Type 1 in which there is a normal population of intraepithelial lymphocytes.
- Type 2 in which there is an aberrant or premalignant population of intraepithelial lymphocytes based upon clonality analysis of T-cell receptors and immunophenotyping. Type 2 can progress to enteropathy-associated T-cell lymphoma, which may present clinically as ulcerative jejunitis [62]. The diagnosis can be established on biopsy; CT and 18F-FDG PET scanning help

identify suspicious areas [66]. (See '[Ulcerative jejunitis and intestinal lymphoma](#)' below.)

Patients with type 1 disease have a less severe presentation and a much better prognosis than patients with type 2 disease [67-70]. Furthermore, type 1 does not appear to evolve into type 2. An illustrative study compared outcomes in 41 patients with type 1 disease to 50 patients with type 2 disease [67]. Five-year survival was higher in the type 1 group (96 versus 58 percent). Most deaths were due to development of T-cell lymphoma (which developed in one-half of patients during follow-up). No patient with type 1 disease developed type 2 disease during an average five years follow-up. A staging system (based upon age, hemoglobin, albumin, the presence of T-cell clones and total villous atrophy) has been proposed and awaits further validation [70].

Refractory sprue (particularly type 2) can be severe and associated with progressive malabsorption and death. A subset of patients develop subepithelial collagen deposition, a condition referred to as "collagenous sprue" [71].

The cause of refractory sprue is unknown. It is possible that some patients with this condition develop sensitivity to a dietary constituent other than gluten. A case report, for example, documented a patient with refractory sprue whose condition normalized after the elimination of eggs, chicken, and tuna in the diet [72]. However, identification of the responsible antigens in most patients is difficult and unrewarding. As a result, treatment has focused on immunosuppression, which has traditionally relied upon glucocorticoids.

The dose of glucocorticoids required varies among patients, and not all patients respond. In severely ill patients, we usually begin with [hydrocortisone](#) (100 mg IV Q6H). Oral dosing (such as 40 to 60 mg of [prednisolone](#) daily) can be used in patients who are tolerating an oral diet. After a few weeks, the dose can be reduced by 5 to 10 mg per day in responding patients and subsequently tapered to the lowest dose that keeps the patient in remission.

Experience with alternative immunosuppressant therapy in patients who require high doses of glucocorticoids is limited to case reports and clinical experience. However, [azathioprine](#) and 6-mercaptopurine appear to be effective steroid-sparing agents [73-75]. (See "[Immunomodulator therapy in Crohn's disease](#)".)

- Oral [budesonide](#) has been effective in case series [76,77].
- A case series described clinical and histologic improvement following treatment with an elemental diet in patients with type 1 refractory sprue [65].
- Another report described remission in a patient with type 2 disease following

treatment with [alemtuzumab](#), an anti-CD52 monoclonal antibody used to treat chronic lymphocytic leukemia [78]. However, the drug was not effective in other reports [79].

- [Cladribine](#) (a synthetic purine nucleoside with cytotoxic activity) was associated with clinical and histologic improvement in 6 of 17 patients with type 2 refractory sprue [80].

**Ulcerative jejunitis and intestinal lymphoma** — Ulcerative jejunitis and lymphoma should be considered in patients with refractory sprue unresponsive to corticosteroids. The conditions are thought to share a similar pathogenesis, since both have aberrant T-cell monoclonality [28,81].

Patients with ulcerative jejunitis have multiple chronic, benign-appearing ulcers, most frequently in the jejunum. Clinical manifestations are similar to severe celiac disease; patients may present with lassitude, anorexia, weight loss, abdominal pain, diarrhea, and fever [82]. Intestinal stricturing can develop with resulting small bowel obstruction. The disease most commonly presents in middle-aged patients with underlying celiac disease.

Ulcerative jejunitis responds poorly to a gluten-free diet and is associated with an unfavorable prognosis. Up to one-third of patients die from complications. The prognosis can be improved if the ulcerated or strictured segment can be resected.

In patients with lymphoma, the histology of adjacent intestine is often indistinguishable from untreated celiac disease. However, it remains uncertain whether these patients had occult celiac disease that became evident only after lymphoma developed, or whether the lymphoma caused the development of celiac-like histology [83].

Intestinal lymphomas in patients with celiac disease are T-cell derived. One study estimated that the risk was increased about fourfold compared with the general population (OR 3.84, 95% CI 2.28-6.45) but that the risk had declined significantly during the last forty years [69]. In addition, the risk appeared to be increased in patients with a sibling with celiac disease. Because T-cell lymphomas of the intestine are far less common than B-cell lymphomas and are usually seen in the context of celiac disease, they have been referred to as "enteropathy-associated T-cell lymphoma." (see "[Clinical manifestations, pathologic features, and diagnosis of enteropathy-associated T-cell lymphoma](#)" and "[Management of gastrointestinal lymphomas](#)", section on 'Enteropathy-associated T-cell intestinal lymphoma').

Lymphoma should be suspected in patients with celiac disease presenting with the clinical features described above for ulcerative jejunitis. Among patients who initially responded to a gluten-free diet, the diagnostic dilemma is whether the return of symptoms is due to dietary lapses or the development of lymphoma.

Clinical manifestations more suggestive of lymphoma, such as fever, hepatomegaly, splenomegaly, duodenal mass(es), or ascites, may help the diagnostic conundrum, but their presence implies more advanced disease. Other presentations of lymphoma include acute perforation, gastrointestinal obstruction, or, less commonly, gastrointestinal hemorrhage.

A full-thickness intestinal biopsy may be required to establish the diagnosis in patients in whom clinical suspicion is high, but radiographic and endoscopic testing is inconclusive. These lymphomas are almost always of high-grade histology and the prognosis is poor. Five-year survival is approximately 10 percent, with the worst outcomes in patients with previously diagnosed celiac disease [84].

Favorable outcomes with multidrug therapy occur only in patients who have minimal gastrointestinal symptoms prior to the diagnosis of lymphoma, and can tolerate therapy [84]. Patients should also be maintained on a gluten-free diet.

**Dermatitis herpetiformis** — Celiac disease is associated with a number of skin disorders, of which dermatitis herpetiformis is the most common (table 3) [85]. Dermatitis herpetiformis is characterized by an itchy papular vesicular eruption usually located symmetrically on the elbows, knees, buttocks, sacrum, face, neck, trunk, and occasionally within the mouth (picture 1 and picture 2). The predominant symptoms are itching and burning that are rapidly relieved with rupture of the blisters.

The earliest abnormality comprises a small erythematous macule 2 to 3 mm in diameter that quickly develops into a papule. Small vesicles then appear to coalesce. Scratching causes them to rupture, dry up, and leave an area of pigmentation and scarring. The diagnosis can be confirmed by the demonstration of granular IgA deposition in the skin in an area not affected by blistering.

Improvement in dermatitis herpetiformis following withdrawal of gluten may be considerably delayed (6 to 12 months) compared to the response of the intestinal manifestations of the disease [86]. As a result, treatment usually includes medical therapy (such as dapsone) in addition to gluten avoidance [85].

**SCREENING FAMILY MEMBERS** — Relatives of patients with celiac disease are at increased risk for having celiac disease [87-90]. The risk is highest among monozygotic twins (approximately 75 percent) [89], HLA-identical siblings (approximately 40 percent) [89], and 17 percent among first-degree relatives of families with at least two affected siblings [87]. Among first-degree relatives, the risk has varied from 5 to 11 percent in various reports [90]. In one report, the risk was highest among male siblings, almost one-half of whom had clinically silent celiac disease despite severe intestinal villous atrophy [90]. In addition, 33 percent of children and 18 percent of parents had celiac disease. Thus, screening of first-

degree relatives (particularly siblings) should be considered. (See "[Diagnosis of celiac disease](#)", section on 'Individuals with a moderate or high risk for celiac disease'.)

**INFORMATION FOR PATIENTS** — Educational materials on this topic are available for patients. (See "[Patient information: Celiac disease in adults](#)".) We encourage you to print or e-mail this topic review, or to refer patients to our public web site, [www.uptodate.com/patients](http://www.uptodate.com/patients), which includes this and other topics.

**SUMMARY AND RECOMMENDATIONS** — There are six key elements in the management of patients with celiac disease, which can be summarized with the acronym CELIAC:

Consultation with a skilled dietitian

Education about the disease

Lifelong adherence to a gluten-free diet

Identification and treatment of nutritional deficiencies including iron, calcium, phosphorus, folate, B12, and fat-soluble vitamins. Patients should also undergo screening for osteoporosis.

Access to an advocacy group

Continuous long-term follow-up by a multidisciplinary team

- We suggest that patients with celiac disease be referred to a dietitian who is familiar with counseling patients on a gluten-free diet. Providing written information and referral to a support group can also be helpful. (See "[Patient information: Celiac disease in adults](#)".)
- The patient's overall nutritional status should be considered so that nutritional and caloric deficiencies can be adequately supplemented. (See "[Clinical features and diagnosis of malabsorption](#)".) Specific dietary deficiency such as iron, [folic acid](#), calcium, vitamin D and, rarely, vitamin B12 deficiency should be corrected. (See "[Overview of the treatment of malabsorption](#)".) A gluten-free diet may induce troublesome constipation since it is low in roughage. This usually responds to the addition of dietary rice bran and ispaghula husks.
- Patients should be educated about the condition and the importance of adhering to a gluten-free diet. We recommend that patients with serologically and histologically confirmed celiac disease and compatible clinical or laboratory manifestations adhere to a gluten-free diet (**Grade 1A**). As noted above, there is some debate about the need for strict gluten avoidance in asymptomatic patients, particularly those in whom celiac disease was detected by serologic screening. There are no large, well designed controlled trials



evaluating the long-term effects of a gluten-free diet in such patients, especially considering issues such as quality of life. However, we suggest strict gluten avoidance in all patients with histologically confirmed celiac disease for the reasons described above (**Grade 2C**). (See ['Is strict gluten avoidance necessary?'](#) above.)

- Bone loss (principally osteopenia and less often osteoporosis) is common in celiac disease, and can occur in patients without gastrointestinal symptoms. (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults"](#).) Much of the bone loss is related to secondary hyperparathyroidism, which is probably due to vitamin D deficiency. It can only be partially reversed with a gluten-free diet. Patients diagnosed with celiac disease should be evaluated for bone loss using a DEXA (dual energy x-ray absorptiometry) scan and appropriate therapy instituted based upon the results. (See ['Prevention of bone loss'](#) above.)
- We suggest that patients with celiac disease receive pneumococcal vaccine since celiac disease is associated with hyposplenism (**Grade 2B**). (See ["Pathogenesis, epidemiology, and clinical manifestations of celiac disease in adults"](#).)
- The need for a follow-up biopsy in patients with clinical improvement has been debated, especially since serologic testing can be used to monitor recovery and compliance with the diet (see ["Diagnosis of celiac disease"](#)). However, we suggest that a repeat small intestinal biopsy be obtained three to four months after beginning a gluten-free diet to demonstrate histologic improvement (**Grade 2C**). If improvement in small intestinal morphology is not seen, but symptomatic improvement has occurred, the diet should be continued and the small intestinal biopsy should be repeated after six to nine months. (See ['Monitoring the response to a gluten-free diet'](#) above.)
- The majority of patients with celiac disease respond to a gluten-free diet. The most common reasons for a lack of response are poor compliance or inadvertent gluten ingestion ([table 1](#)). Thus, we suggest a meticulous dietary history should be obtained, and dietary counseling pursued with an experienced dietitian in patients who continue to have symptoms or persistent histologic abnormalities, or in those in whom serum antibody titers have not declined.
- Patients who do not respond despite adherence to a gluten-free diet fall into three main categories, those with: clinical or histologic features that are caused by other disorders; refractory sprue; ulcerative jejunitis or intestinal lymphoma. (See ['Nonresponders'](#) above.)



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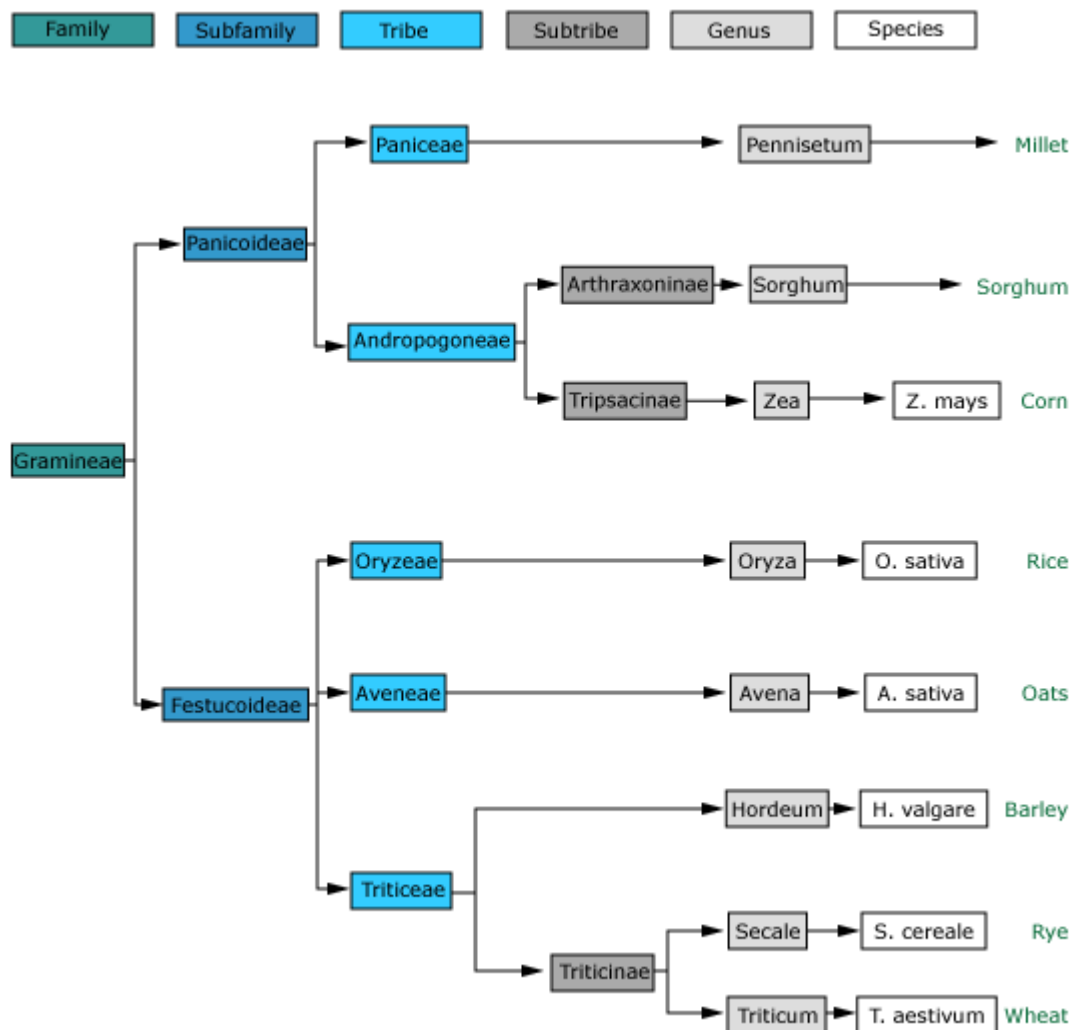
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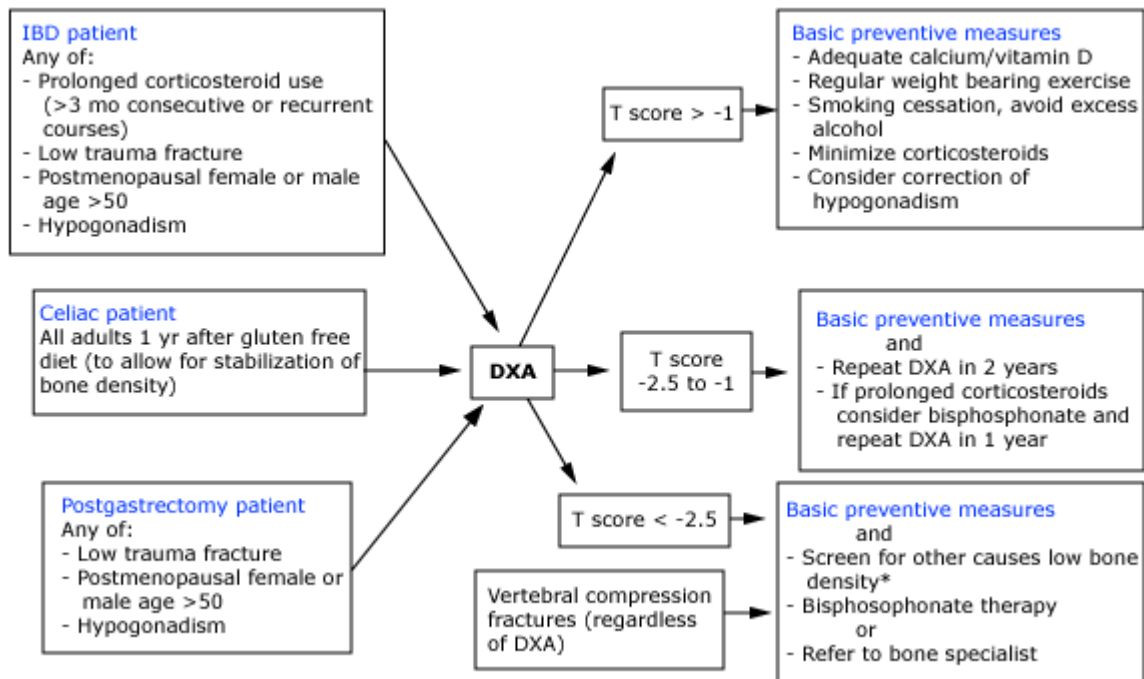
## GRAPHICS

### Taxonomic relationships of major cereal grains



Adapted from Kasarda, DD, *Proc Natl Acad Sci U S A* 1984; 81:4712.

## A management approach for osteoporosis in gastrointestinal diseases



\* Complete blood count, serum calcium, alkaline phosphatase, creatinine, 25-OH-vitamin D, protein electrophoresis, testosterone (males). *Reproduced with permission from: the American Gastroenterological Association. Bernstein, CN, Leslie, WD, Leboff, MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology 2003; 124:795.*



## Foods and products that may contain gluten

Frequently overlooked foods that may contain gluten and need to be verified:	NOT ALLOWED in any form:
Brown rice syrup	Wheat (einkorn, durum, faro, graham, kamut, semolina, spelt)
Breading and coating mixes	Rye
Croutons	Barley
Energy bars	Triticale
Flour or cereal products	Malt, malt flavoring, malt vinegar (are generally made from barley, verify the source)
Imitation bacon	
Imitation seafood	
Marinades	
Panko (Japanese bread crumbs)	
Pastas	
Processed luncheon meats	
Sauces, gravies	
Self-basting poultry	
Soy sauce or soy sauce solids	
Soup bases	
Stuffings, dressing	
Thickeners (roux)	
Communion wafers	
Herbal supplements	
Drugs and over-the-counter medications	
Nutritional supplements	
Vitamins and mineral supplements	

Play-dough, crayons, paint, glue, paper mache:  
A potential problem if the child puts their hands  
on or in the mouth while playing. Wash hands  
after using these products.

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## Causes of small intestinal villous atrophy other than celiac disease

Bacterial overgrowth
Crohn's disease
Cow's milk protein intolerance (children)
Eosinophilic gastroenteritis
Giardiasis
Lymphoma
Peptic duodenitis
Post gastroenteritis
Tropical sprue
Zollinger-Ellison syndrome
Common variable immunodeficiency
Autoimmune enteropathy
Other immunodeficiency states (usually apparent clinically)

## Skin disorders associated with celiac disease

Acquired ichthyosis
Cutaneous amyloid
Cutaneous vasculitis
Dermatitis herpetiformis
Eczema
Epidermal necrolysis
Nodular prurigo
Pityriasis rubra pilaris
Pustular dermatitis

## Dermatitis herpetiformis



Herpetiform clusters of vesicles on an erythematous, edematous base with crusts and postinflammatory pigmentation on the upper back and shoulder. *Reproduced with permission from: Skin signs of immune, autoimmune, and rheumatic diseases. In: Color Atlas and Synopsis of Clinical Dermatology, 3rd ed, Fitzpatrick, TB, Johnson, RA, Wolff, K (Eds), McGraw-Hill, New York 1997. p.327. Copyright © 1997 McGraw Hill.*

## Dermatitis herpetiformis

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A skin blister on the elbow of a subject with dermatitis herpetiformis. *Reproduced with permission from the American Gastroenterological Association. Ciclitira, PJ. Gastroenterology 2001; 120:1526.*

